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Affecting FDA-Regulated Products*

What Will It Take to Reap the Clinical Benefits of Pharmacogenomics?

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I. INTRODUCTION

Pharmacogenetics and pharmacogenomics explore why two patients who take the same medicine may respond differently, reflecting individual differences in genes that affect disease susceptibility, disease characteristics, or the patients' ability to metabolize drugs.¹ Personalized medicine seeks to harness this knowledge by using genetic and other *in vitro* diagnostic tests to determine, before a prescription is written, whether the patient belongs to a population subgroup that should take the drug, avoid the drug, or take it in an adjusted dosage. The term "targeting" also is used to refer to this concept of basing treatment choices on a patient's particular molecular, genetic, disease, or metabolic characteristics.

Genetic variability of drug response was first suspected in the 1950s,² but it is only in the past decade that pharmacogenomics gained enough explanatory power to offer real prospects of improving medical care. There has been some frustration with the slow pace at which basic pharmacogenomic discoveries are being translated into clinically useful products and treatment methods.³ This frustration may simply be a response to optimistic hyperbole that surrounded completion of the Human Genome Project several years ago, when personalized medicine was sometimes presented as being closer to clinical introduction than it actually was. Legal scholars and ethicists embraced person-

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¹ See, e.g., The European Agency for the Evaluation of Medicinal Products (EMA), Committee for Proprietary Medicinal Products, POSITION PAPER ON TERMINOLOGY IN PHARMACOGENOMICS (EMA, Report No. EMA/CPMP/3070/01, London, (2002)), at www.emea.eu.int/pdfs/human/press/pp307001en.pdf; L.J. Lesko, R.A. Salerno, B.B. Spear, et al., *Pharmacogenetics and Pharmacogenomics in Drug Development and Regulatory Decision Making: Report of the First FDA-PWG-PhRMA-DruSafe Workshop*, 43 J. CLIN. PHARMACOL. 342, 343 (2003); Nuffield Council on Bioethics, PHARMACOGENETICS: ETHICAL ISSUES (Nuffield Council on Bioethics, London, (2003)), at http://www.nuffieldbioethics.org/go/ourwork/pharmacogenetics/publication_314.html; T.E. Klein, J.T. Chang, M.K. Cho, et al., *Integrating Genotype and Phenotype Information: An Overview of the PharmGKB Project*, 1 THE PHARMACOGENETICS J. 167 (2001); F.S. Collins, E.D. Green, A.E. Guttman, & M.S. Guyer, *A Vision for the Future of Genomics Research*, 422 NATURE 835, 840-2 (2003).

² Russ B. Altman, INTRODUCTION TO PHARMACOGENOMICS, SL. 23, 1950's/60's classic PGx examples, at <http://www.pharmgkb.org/resources/education/tutorials.jsp>.

³ Lawrence J. Lesko & Janet Woodcock, *Translation of Pharmacogenomics and Pharmacogenetics: A Regulatory Perspective*, 3 NATURE REVIEWS 763, 767 (2004); B.J. Evans, D.A. Flockhart, & E.M. Meslin, *Creating Incentives for Genomic Research to Improve Targeting of Therapies*, 10 NATURE MEDICINE 1289 (2004); Stuart Hogarth, Kathy Liddell, Tom Ling, et al., REGULATING PHARMACOGENOMICS: AN OVERVIEW OF DEVELOPMENTS IN VARIOUS COUNTRIES AND INDUSTRY RESPONSE TO REGULATORY INITIATIVES: A REPORT FOR HEALTH CANADA (Cambridge, (2006)), at 7.

alized medicine and debated its broader societal implications, such as discrimination and distributional impacts on the poor, even as pharmacologists still were debating its basic clinical feasibility. Five years ago, one could fairly state that the legal debate was running ahead of the science.

More recently, this situation has begun to change. Pharmacogenomics is delivering a small but steady stream of approved medical products, and a growing list of pharmaceutical and medical device manufacturers is investing in pharmacogenomic research. Academic scientists continue to play an important role in this field, but they are no longer alone and, indeed, may no longer account for the majority of research activity and expenditures. There is a sense that the science of pharmacogenomics, after frustrating delays, finally is poised to have real clinical significance. The legal debate is shifting from speculative problems to real ones. As summarized in a recent Health Canada report on pharmacogenomics, "There is now a general consensus that progress will be much slower than was first hoped and much activity is now focused on understanding why this is and what can be done about it."⁴

This article explores a group of regulatory problems that, if not solved, may slow the pace at which personalized medicine moves into wide clinical use. In the past decade, various studies were carried out in the United States⁵ and around the world to develop appropriate policies for regulation of genetic testing.⁶ Recommendations from these studies tended to address genetic testing in a general manner, and there is a need to refine the analysis and explore issues specific to particular types of genetic test. The genetic tests used in personalized medicine present distinct medical, economic, ethical, legal, and regulatory issues. Moving these tests into the clinic and ensuring their safe, effective use may require innovative regulatory approaches, new types of oversight bodies, and new ways of involving the medical and scientific communities in the regulatory process.

For ease of reference, we will refer to the class of genetic tests used in personalized medicine as "treatment-adaptive biomarker" tests (TAB tests). They detect biomarkers (genes, proteins, and chemicals present in the human body), in response to which the course of a patient's treatment may need to be adapted by selecting or avoiding particular drugs or biologic therapies (collectively, "drugs"), by adjusting the dose, or by taking special steps to manage risks after a drug is administered. TAB tests include predictive genetic tests, such as drug-metabolizing enzyme genotyping systems that detect markers for genes that encode specific enzymes that affect a patient's response to particular drugs. TAB tests also include tests for specific molecular targets on which

⁴ Hogarth *et al.*, *supra* note 3, at 7.

⁵ See, e.g., Joint National Institutes of Health (NIH)—Department of Energy (DOE) Ethical, Legal and Social Implications Working Group of the Human Genome Project, Task Force on Genetic Testing, PROMOTING SAFE AND EFFECTIVE GENETIC TESTING IN THE UNITED STATES (N.A. Holtzman & M.S. Watson, eds., (Sept., 1997)), at <http://www.genome.gov/10002404>, see ch. 2; NIH, Secretary's Advisory Committee on Genetic Testing, ENHANCING THE OVERSIGHT OF GENETIC TESTS: RECOMMENDATIONS OF THE SACGT (July, 2000) at <http://www4.od.nih.gov/oba/sacgt/gtdocuments.html>, see Executive Summary at x; Dep't. of Health & Human Servs. (HHS), *Establishment of the Secretary's Advisory Committee on Genetics, Health, and Society*, 67 Fed. Reg. 65,126 (Oct. 23, 2002).

⁶ See, e.g., U.K. Human Genetics Commission, GENES DIRECT: ENSURING THE EFFECTIVE OVERSIGHT OF GENETIC TESTS SUPPLIED DIRECTLY TO THE PUBLIC (Human Genetics Commission, London, (Mar., 2003)), at <http://www.hgc.gov.uk/client/Content.asp?ContentId=266>; Stuart Hogarth, David Melzer & Ron Zimmern, THE REGULATION OF COMMERCIAL GENETIC TESTING SERVICES IN THE UK: A BRIEFING FOR THE HUMAN GENETICS COMMISSION (Cambridge, (2005)), at <http://www.hgc.gov.uk/Client/document.asp?DocId=97&CAtagoryId=8>; World Health Org. (WHO), *Quality & Safety in Genetic Testing: An Emerging Concern*, at <http://www.who.int/genomics/policy/en/>; Organization for Economic Co-operation and Development (OECD), *Genetic Testing: Policy Issues for the New Millennium* (2001), at http://www.oecd.org/document/16/0,2340,en_2649_37407_1895632_1_1_1_37407,00.html; OECD, *Quality Assurance and Proficiency Testing for Molecular Genetic Testing: Survey of 18 OECD Member Countries* (2005), at www.oecd.org/dataoecd/25/12/34779945.pdf.

certain drugs operate, such as the estrogen receptor for tamoxifen or the HER-2 protein for trastuzumab. Not all TAB tests are genetic tests, strictly speaking, since some detect phenotypic expressions of genes that are present either in the patient, in the patient's tumor, or in the disease-causing virus or bacterium.

Although TAB tests may differ in their scientific properties, they pose a common set of regulatory problems. These problems often can be traced to: a) novel patterns of discovery and development in the field of pharmacogenomics; b) the still-undefined role that targeted therapies will play in future clinical practice; and c) unique technical characteristics of targeted therapeutic products themselves. The novelty of these problems, at times, has made them difficult to spot, creating a risk that well intentioned policy-development efforts will solve perceived problems in lieu of the real ones. Consensus solutions cannot be achieved, without consensus on what the problems are.

There has been a persistent failure to grasp how profoundly pharmacogenomics strains the existing regulatory paradigm for development, validation, approval, clinical introduction, and use of new medical technologies. This paradigm dates to the mid-twentieth century and was designed to promote the safety and effectiveness of medical technologies then under development.⁷ Targeted therapies explode this paradigm in a variety of ways, discussed in this article, and they pose new regulatory challenges that will require many good minds and much good data to overcome. This article aims to stimulate debate about what the problems are, and it identifies near-term steps to lay groundwork for solutions.

II. MULTIPLE MODES OF DISCOVERY AND NON-TRADITIONAL PRODUCT DEVELOPMENT PATHWAYS FOR TARGETED THERAPIES

A. *The Need to Accommodate Multiple Discovery and Development Pathways*

There are three distinct scenarios for discovery of a targeted therapy, depending on when the targeting strategy (i.e., the pharmacogenetic targeting principle or the molecular target on which a drug acts) is discovered, relative to discovery and development of the drug:

- prospective co-development of a drug and TAB test, based on a targeting strategy discovered early in drug development;
- discovery of a targeting strategy late in clinical trials of the drug, necessitating a revised development path if the drug and test are going to be offered for use together; and
- post-market discovery of a targeting concept for a previously approved drug.

Clear regulatory-approval pathways are needed for products that flow from all three of these discovery scenarios.

Many nations, including the United States, rely on drug regulations that were designed in the mid-twentieth century. Premarket review of drug safety in the United States dates back to passage of the Food, Drug, and Cosmetic Act (FDCA) in 1938,⁸ which was amended in 1951 to distinguish between prescription and over-the-counter drugs,⁹ and

⁷ B.J. Evans & D.A. Flockhart, *The Unfinished Business of U.S. Drug Safety Regulation*, 61 THE FOOD & DRUG L. J. 45 (2006).

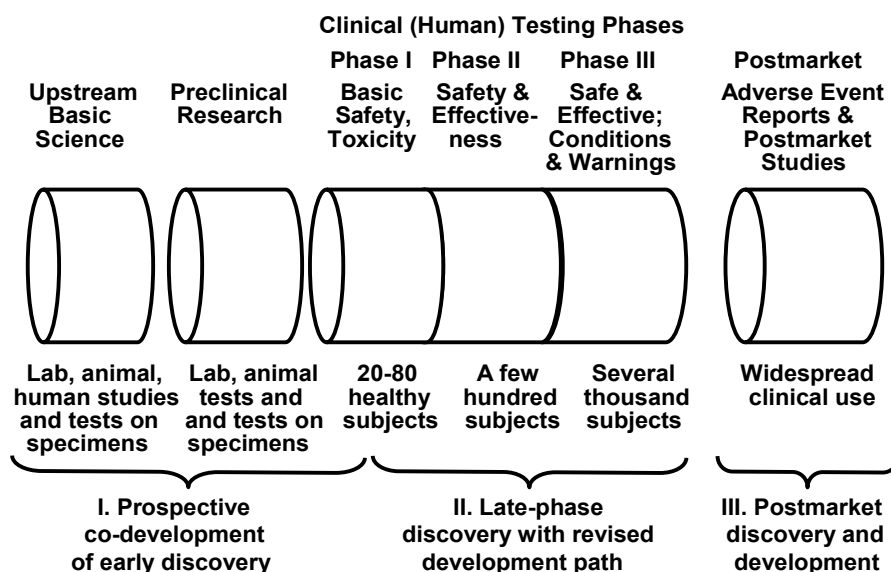
⁸ FDCA, Pub. L. No. 75-717, 52 Stat. 1040 (1938), as amended (codified at 21 U.S.C. §§ 301-399).

⁹ Durham-Humphrey Act, Pub. L. No. 82-215, 65 Stat. 648 (1951).

again in 1962 to require premarket review of efficacy as well as safety.¹⁰ This basic framework was designed to accommodate the discovery pathways that yielded yesterday's medical products. It presumes an orderly sequence of events in product development, with discovery preceding preclinical research, clinical testing, and product approval (See Figure 1). Pharmacogenomic discoveries may occur "out of order," and the resulting clinical products may not fit well into the existing approval pathways.

Scenario I (prospective co-development of a drug and a TAB test) meshes fairly well with the traditional product-approval pathway. Trastuzumab (HerceptinTM) is an example of a biologic therapy for which the targeting strategy was discovered early in the product development cycle.¹¹ Its manufacturer entered an agreement with a molecular diagnostics manufacturer to develop a screening test to use in targeting the therapy. The two products were approved by the Food and Drug Administration (FDA) in separate, but coordinated, biologics licensing and device approvals granted on the same day.¹²

Figure 1
Phases of Drug Development



In 2005, FDA circulated a draft concept paper¹³ to clarify issues related to prospective co-development of drugs and TAB tests (Scenario I). A number of industry comments objected that Scenario I may not be the most likely discovery scenario in actual practice, since the mechanisms that would let a drug be targeted often are not discovered until drugs are tested on a large number of people during late-phase clinical trials (Phase

¹⁰ Drug Amendments of 1962, Pub. L. No. 87-781, 76 Stat. 780 (1962).

¹¹ Genentech, HerceptinTM (Trastuzumab) Development Timeline, at <http://www.gene.com/gene/products/information/oncology/herceptin/timeline.jsp>.

¹² *Id.*; see also, FDA, *New Monoclonal Antibody Approved for Advanced Breast Cancer* (News release P98-27, (Sept. 25, 1998)).

¹³ HHS, FDA, *Drug-Diagnostic Co-Development Concept Paper* (April, 2005), at <http://www.fda.gov/cder/genomics/pharmacconceptfn.pdf>.

II/III trials).¹⁴ These comments suggest that industry sees Scenario II as a likely mode of discovery for new targeted therapies.

A third possible scenario is that a targeting strategy may be discovered *after* a drug has received FDA approval and is in wide clinical use.¹⁵ There already have been many discoveries of this type. The first FDA-approved Cytochrome P450 (CYP-450) test became available in 2004 after numerous research studies explored the role of this enzyme in metabolizing a variety of FDA-approved drugs.¹⁶ Unexplained variations in patients' responses to older drugs may later be traced to genetic factors that affect drug metabolism. This has occurred, for example, with the decades-old cancer drug 6-mercaptopurine; azathioprine and 6-thioguanine; irinotecan; and the widely prescribed blood-thinning drug warfarin.¹⁷ Molecular targeting strategies are also subject to late discovery. For example, the long-used, nonspecific cyclophosphamide, methotrexate, and fluorcil (CMF) chemotherapy regimen recently was found to be highly effective for a targeted population of patients identified through use of multigene reverse transcriptase PCR technology to estrogen receptor-positive, lymph node negative breast cancer.¹⁸

Policy development must begin with a clear understanding of how pharmacogenomic discovery and development actually work (i.e., how common each of the three discovery scenarios has been in actual practice to date, and how common each discovery scenario is likely to be in the future). This information is needed to guide regulators in developing appropriate processes for approving targeted therapies and TAB tests. If Scenarios II and III are expected to account for the lion's share of pharmacogenomic discoveries, then high priority should be placed on identifying and addressing regulatory issues that these discovery scenarios present. If Scenario I is expected to account for most targeted therapies in the future, then a focus on prospective drug/test co-development may be appropriate.

Historical discovery patterns could be clarified using publicly available data, such as the Pharmacogenetics and Pharmacogenomics Knowledge Base (PHARMGKB),¹⁹ funded by the National Institutes of Health (NIH). THE PHARMGKB database currently contains information on 385 drugs and various gene-drug, gene-disease, and gene-drug-disease associations and describes the type of evidence that is available to support these associations. For drugs with known genetic variations in patient response, the relevant discovery scenario can be deduced through a review of scientific literature and interviews with persons involved in discovering the biomarkers that are predictive of patient response to each such drug. A rough forecast of future discovery scenarios could be developed by surveying the types of research now underway. If numerous studies are underway to explore differential patient response to drugs that already are FDA-approved, this would tend to suggest that Scenario III discoveries may be common in coming years. It is critical to design regulatory approval pathways that correspond to the actual flow of discoveries in the field of pharmacogenomics.

¹⁴ Letter from Robert Yocher, Genzyme Corp., to FDA (July 15, 2005), p. 1; Letter from Sue T. Hall, GlaxoSmithKline, to FDA (June 30, 2005), *see* attached Comments, § 6, p. 4; Letter from Carolyn D. Jones, Advanced Medical Technology Association (AdvaMed), to FDA (July 15, 2005), p. 2.

¹⁵ G.W. Sledge, *What is targeted therapy?* 23 JOURNAL OF CLINICAL ONCOLOGY 1614, 1614-15 (2005).

¹⁶ FDA, *New Device Clearance: Roche AmpliChip Cytochrome P450 Genotyping tests and Affymetrix GeneChip Microarray Instrumentation System—K042259*, at <http://www.fda.gov/cdrh/mda/docs/k042259.html>; *see also*, Information on CYP2D6 allele nomenclature, at <http://www.imm.ki.se/CYPalleles/cyp2d6.htm>, and Brief description of Cytochrome P4502D6, at <http://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=124030>.

¹⁷ Lesko & Woodcock, *supra* note 3, at 767.

¹⁸ Sledge, *supra* note 15, at 1614.

¹⁹ Pharmacogenetics and Pharmacogenomics Knowledge Base, at <http://www.pharmgkb.org/>; *see, generally*, Klein *et al.*, *supra* note 1, for a description of this database.

B. Barriers to Clinical Translation of Scenario II Discoveries (Discovery of a Targeting Strategy during Late-phase Clinical Trials)

There appear to be serious problems translating Scenario II discoveries (discoveries made during late-phase clinical trials) into new targeted therapies. When genetic variability of drug response is discovered late in clinical trials, the business outcome often is drug development failure (i.e., attrition of the drug from any further development). This contrasts with earlier hope that pharmacogenomics would let such drugs be “rescued,” i.e., let the drugs be recast as targeted therapies for genetically defined subpopulations, when late-phase trials fail to demonstrate safety and effectiveness for the trial population at large.²⁰ To date, there have been few, if any, actual examples of drug rescue in which a Scenario II discovery made it to the market as a new targeted therapy.²¹ Just how common these problems are, and what is causing them, is not well understood.

To inform policy in this area, there is a need for postmortem studies of cases where targeting strategies have been discovered late in clinical drug trials (Scenario II discoveries), including cases that ended in drug development failure and cases (if any) where the drug was subsequently brought to market as a targeted therapy. What commercial alternatives did manufacturers and regulators consider in each case? Did they consider pressing forward with approval of the drug for untargeted use, perhaps with a warning that patient response may vary based on genetic factors? Did they consider developing the drug further for targeted use in a narrow subpopulation? What factors drove the final decision? Can the barriers to clinical introduction be addressed through appropriate policies?

Multiple factors may be contributing to the slow clinical translation of Scenario II discoveries. These factors may include perceived ethical and liability issues of bringing a drug to market, when there is a suspected genetic variability in drug response that is not yet known to be valid. Informed consent law and medical practice regulations may need to be modernized to address new issues that pharmacogenomics presents (e.g., should patients’ informed consent be required for drugs that have a suspected, but uncertain, genetic variability in response? Who should be liable for drug injuries arising from physicians’ off-label use of a targeted drug in subpopulations for which it was not intended?) At present, there are no clear rules for assessing the legal impact of a biomarker’s validation status. Just how strong does the association between genotype and drug response need to be, to take on various types of legal significance (e.g., to justify holding a physician liable for prescribing the drug without ordering a TAB test, or to justify denying approval of a drug until there is a screening test available for clinical use)? This legal uncertainty may be chilling development of new targeted therapies. It calls for thorough review of state statutes, state case law,

²⁰ See, e.g., Mark A. Rothstein & Phyllis Griffin Epps, *Ethical and Legal Implications of Pharmacogenomics*, 2 NATURE REVIEWS GENETICS 228, 228 (2001); Barbara Ann Binzack, *How Pharmacogenomics Will Impact The Federal Regulation of Clinical Trials and the New Drug Approval Process*, 58 THE FOOD & DRUG L. J. 103, 113 (2003).

²¹ BiDil™, a combination of hydralazine and isosorbide dinitrate was approved for treatment of heart failure in self-identified African American patients in 2005; however, it is not an example of a targeted therapy in the true sense, since the genetic targeting mechanism was still unknown at the time of approval. See FDA, *FDA Approves BiDil Heart Failure Drug for Black Patients* (News release P05-32, (June 23, 2005)), at <http://www.fda.gov/bbs/topics/NEWS/2005/NEW01190.html>.

and FDA regulations and guidance documents to assess where the uncertainties lie and how they can be clarified.

Commercial problems no doubt seal the fate of many Scenario II discoveries. If a drug is only safe and effective for a narrow subpopulation, the remaining market may be too small to be of commercial interest. The needed TAB test may exist in the laboratory but not yet be commercially available. When a targeting strategy is discovered late in clinical trials, further trials may be needed to verify that the drug is safe and effective in the targeted subpopulation. These trials may be unacceptably costly or may pose problems with remaining patent life, since only half the time spent performing human clinical trials is restored to a drug's patent life under Hatch-Waxman.²²

The legal literature on drug rescue²³ has not fully addressed how hard it can be to draw valid statistical inferences from an earlier, negative clinical trial that has failed to establish hoped-for levels of safety and effectiveness in the trial population at large. Suppose a drug has been tested in a general population that included people with many different hair colors, and has produced good results in the subgroup of patients who are redheads. This does not prove that the drug is safe and effective for targeted use in redheads. The apparent association, which was spotted retrospectively after patients' individual responses to the drug were known, may be pure coincidence. A new, prospective clinical trial in redheads is likely to be needed, to validate the suspected association. Selection bias and other research-design issues may make it impossible to draw statistically valid conclusions from the clinical trials that already took place. Drug rescue is not free, in the sense that a targeted therapy can simply be plucked from the sea of data already on hand. The costs of redeveloping a drug for use in a screened patient subpopulation may simply be too high to yield an economically viable targeted therapy.

As these challenges are better understood, policy solutions may be available. FDA already has work underway to develop guidelines for adaptive clinical trials, in which information about patient outcomes early in a clinical trial could be used to adjust later segments of the trial, while still maintaining a basis for good statistical decisions.²⁴ Additional regulatory solutions may be needed for cases where targeting strategies are discovered late in clinical trials. For example, a special approval pathway—similar to FDA's accelerated approval program²⁵—could let such drugs be approved for targeted use based on a suspected gene-drug association, subject to postmarket study requirements to validate the targeting strategy. Size-of-market problems might be addressed through special incentives, such as an enhanced version of the orphan drug program²⁶ for pharmacogenomic discoveries that doom a drug to a narrowly targeted future market. A special patent-term extension may be warranted for drugs that require a second round of clinical trials to validate a late-discovered targeting strategy. There also may be a role for direct public funding of research to complete the development of promising targeted therapies that are not commercially viable. The first step is to develop a better practical understanding of what, exactly,

²² 35 U.S.C. § 156(g).

²³ Rothstein & Epps, *supra* note 20; Binzak, *supra* note 20.

²⁴ See, e.g., 2006 CONFERENCE ON ADAPTIVE TRIAL DESIGN (July 10, 2006), at <http://www.fda.gov/oc/speeches/2006/trialdesign0710.html>. See, Presentation of Scott Gottlieb, Deputy Commissioner for Medical and Scientific Affairs, FDA.

²⁵ 21 C.F.R. Pt. 314, Subpt. H (§§ 314.500-314-560); Pt. 601, Subpt. E (§§ 601.40-601.46).

²⁶ 21 C.F.R. Pt. 316 (§§ 316.2 – 316.52).

is impeding the clinical translation of Scenario II discoveries, so that appropriate policy solutions can be crafted.

C. Barriers to Translation of Scenario III Discoveries (Discovery of a New Targeting Strategy after a Drug Is Approved)

Sledge has pointed out that any therapy that works must have a molecular target; untargeted drugs are merely the cases where scientists discovered the drug before they discovered the target.²⁷ As already noted, there are many examples where variable patient responses to an older, marketed drug were later found to have a genetic explanation. This prevalence of postmarket (Scenario III) discoveries in pharmacogenomics may reflect a pattern that will continue in the future or it may simply be a historical artifact. Academic scientists dominated pharmacogenomic research in its early years, and this may have focused pharmacogenomic studies on approved drugs, since approved drugs are in wide use and are readily available for academicians to study. This effect may have biased the early research in favor of Scenario III discoveries. As drug manufacturers increasingly take up the search for gene-drug interactions, and as pharmacogenomic studies are incorporated into earlier phases of the drug-development cycle, the prevalence of Scenario I and Scenario II discoveries may increase in coming years. However, Scenario III discoveries are likely to remain important, so long as regulations allow approval of drugs that exhibit significant, unexplained variations in patient response. Everything that remains unknown about safety and effectiveness at the moment of drug approval—and that is quite a lot—serves as fodder for Scenario III discoveries. Moreover, some gene-drug interactions are rare and only show up when a drug is taken by large numbers of people—i.e., after drug approval.

FDA believes there is value in applying pharmacogenomic principles to older, marketed drugs to improve their risk-benefit ratios by optimizing or individualizing dosing.²⁸ However, it can be harder to change prescribing practices for an older drug than for a newer drug.²⁹ With older drugs, clinicians may already have worked out procedures for coping with adverse side effects (e.g., using blood tests to monitor whether a patient's white blood cell count is dropping too low). A new genetic test that predicts which patients are at risk for this side effect may offer an unclear cost/benefit ratio, relative to the current procedures, and it may create new risks related to erroneous test results. The available clinical trial data may not be adequate to support a specific recommendation on how to adjust dosages for patients with different genotypes,³⁰ and it may only be possible to give a general warning that patient response varies in response to genetic factors.

A separate set of problems—they could be called cooperation issues—may also be impeding the clinical introduction of new targeting strategies for already-approved drugs. These problems include, for example, a) legal and commercial barriers to cooperation among the multiple, separate parties that may hold intellectual property (IP) rights or other business and ownership interests in the drug, the targeting strategy, and the TAB test; b) FDA's unclear authority to require cross-labeling of TAB tests and drugs, in cases where this would force two separate manufacturers into

²⁷ Sledge, *supra* note 15, at 1614.

²⁸ Lesko & Woodcock, *supra* note 3, at 767.

²⁹ *Id.* at 768.

³⁰ *Id.* at 767.

an unwanted “marriage”; and c) opportunities for drug manufacturers to engage in strategic blocking behaviors, i.e., to obstruct development and regulatory clearance of new TAB tests, in cases where better targeting may erode the market share of an already-approved drug. These cooperation issues are explored in Section VI, *infra*, after necessary background has been laid.

III. PROBLEMS ASSESSING THE CLINICAL BENEFITS OF TAB TESTS AND TARGETED THERAPIES

A. *The Need for a Consensus Concept of Clinical Utility*

TAB tests are intended for use in conjunction with drugs. This makes it difficult to characterize the clinical utility of the test, as distinguished from the utility of the drug itself or of the drug/test combination. Public comments on FDA’s 2005 concept paper on drug-test co-development³¹ sought a clearer definition of what “clinical utility” means in this context and expressed concern that different regulators and courts may assess the benefits of targeted therapies in different ways, e.g., for approving products, for approving Medicare reimbursements, and for defining the clinical standard of care.³²

Inconsistent assessments of clinical benefit can create confusion about the appropriate clinical use of TAB tests and may impede patients’ access to personalized medicine. Physicians and the public will face tough dilemmas, for example, if FDA has approved a TAB test, but insurers and Medicare decline to reimburse it. These dilemmas grow all the more complex if there are several competing tests for the same biomarker, particularly if there is scientific evidence suggesting that a newer, non-FDA-regulated test³³ may be more reliable than an older, FDA-approved test. Appropriate use of screening tests will make drug-related injuries partially but never fully preventable, and causation of drug-related injuries will be even more difficult to decipher than it is today (e.g., was an injury caused by the drug; by the test that erroneously indicated that the patient could safely take the drug; by the physician who failed to order the best available test for making that determination; or by the physician’s failure, after ordering an appropriate test that gave an accurate result, to draw correct conclusions about which drug to prescribe?). The clinical benefits of performing a test and, in particular, the relative benefits of using one test as opposed to another one, will be subject to considerable scientific uncertainty and the appropriate standard of care may be extremely difficult to discern at any point in time. Juries—without knowledge of statistics, genetics, or pharmacology—may be left to decide whether a physician should be held liable for prescribing the drug without first ordering a particular test.

There is a critical need for appropriate, consensus methodologies to evaluate the incremental safety, therapeutic, and economic benefits of using TAB tests to target drugs and biologic therapies. These estimates will be needed to guide a wide variety of policy decisions in coming years (e.g., how much priority to place on pharmacogenomic research and the development of new TAB tests; whether the use of particular

³¹ HHS, FDA, *Drug-Diagnostic Co-Development Concept Paper* (Apr., 2005), *supra* note 13.

³² See, e.g., Letter from Robert Yocher, Genzyme Corp., to FDA (July 15, 2005), p. 2; Letter from Marie A. Vodicka, Pharmaceutical Research and Manufacturers of America (PhRMA), to FDA (July 19, 2005), p. 9; Letter from Carolyn D. Jones, Advanced Medical Technology Association (AdvaMed), to FDA (July 15, 2005), p. 2.

³³ See discussion of non-FDA-regulated tests in Section IV, *infra*.

TAB tests should be funded by governmental and private health plans; whether and when TAB testing should be incorporated into the standard of care; and when the use of a drug, without related TAB testing, should require informed consent or be grounds for malpractice liability). These estimates also are needed to support the development of suitable metrics of clinical performance, for use in assessing whether TAB tests are being appropriately applied so as to deliver their projected benefits.

B. Problems Applying Traditional Regulatory and Legal Standards to TAB Tests and Targeted Therapies

Traditional methods of assessing the safety, effectiveness, and cost-effectiveness of new medical products may not accurately portray the benefits of TAB tests and may inject subtle biases into regulatory, insurance, and judicial decisions. An example of this phenomenon can be seen in FDA's methods for assessing drug safety. The FDCA requires a drug to be "safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof."³⁴ This standard implies a risk-benefit assessment.³⁵ Over the years, FDA and its counterparts in other nations participating in the International Conference on Harmonization (ICH) have developed standard methodologies for conducting this risk-benefit analysis.³⁶ As discussed below, these methodologies inject biases that may favor the approval of badly targeted drugs and preclude accurate assessment of the incremental benefits of a better-targeted therapy.

Figure 2 portrays outcomes experienced in a population of trial participants exposed to a hypothetical new drug. The horizontal axis depicts the population of trial participants and the frequency of various drug responses within that population; the vertical axis depicts the magnitude of patients' benefits and harms. In this example, 10 percent of trial participants were adverse responders who suffered actual injuries, but no benefits, when they took the drug (see area in black at left). Sixty percent of participants were non-responders who neither benefited from, nor were directly injured by, the drug. The remaining 30 percent of trial participants experienced varying levels of therapeutic benefit (see vertically striped area). These people included 10 percent of the trial population who experienced a small benefit but suffered some adverse side effects; 10 percent who experienced small benefits without bad side effects; and 10 percent who received a large therapeutic benefit from the drug.

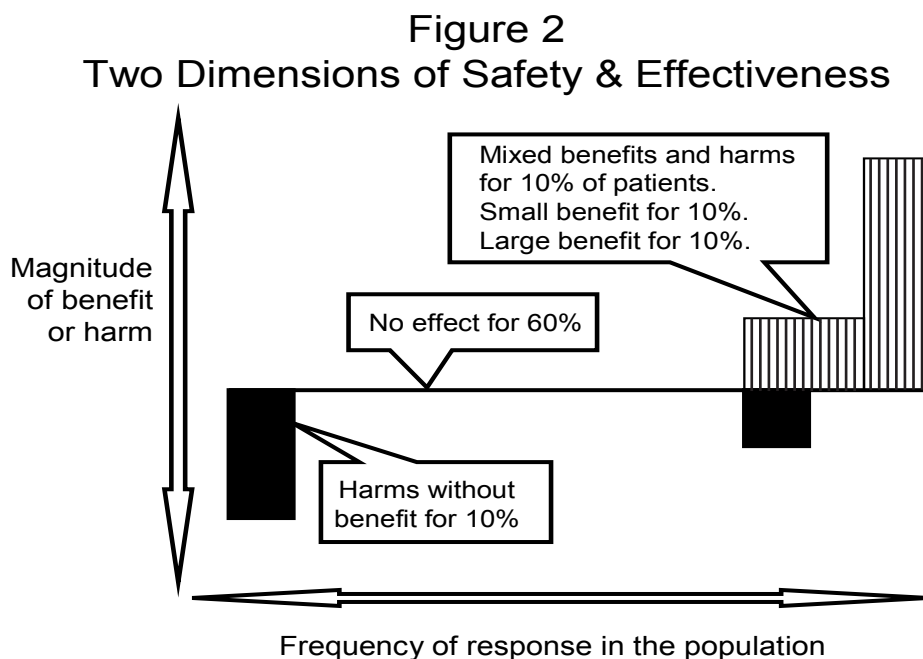
Under the current FDA/ICH methodology, the drug's risk-benefit ratio would be calculated by comparing benefits (as measured by the striped areas in Figure 2) to harms (as measured by the areas in black). Non-response is implicitly reflected in this ratio as a reduction in benefits (i.e., as a lack of effectiveness). However, non-response is not treated as a safety problem in its own right (i.e., as a factor that could itself result in patient injuries). As discussed further below, current FDA/ICH risk-benefit methodology treats non-response as an effectiveness problem, but not a safety problem. In fact, non-response may be both. There can be genuine harms associated with taking a drug that produces no therapeutic benefit. Primarily, these are opportunity costs or

³⁴ FDCA § 505(d), 21 USC § 355(d).

³⁵ Presentation by D.C. Throckmorton, Acting Deputy Director, Center for Drug Evaluation and Research (CDER), *Efficacy Biomarkers: Efficacy/Risk Assessment* (Oct. 6, 2005); see, also, FDA, CDER, CLINICAL REVIEW TEMPLATE (MANUAL OF POLICIES AND PROCEDURES 6010.3), Version 07/09/04, at 7.

³⁶ International Conference on Harmonization (ICH), *Guideline for Industry: Structure and Content of Clinical Study Reports* (INTERNATIONAL CONFERENCE ON HARMONIZATION E3) (July, 1996), at 35; HHS, FDA, *Guidance for Industry: E2E Pharmacovigilance Planning* (Apr., 2005), at 2.

“lost-chance”³⁷ injuries, where the patient is hurt as a result of foregoing other therapeutic options that might have worked. Lost-chance injuries can be permanent and life-threatening, e.g., if the patient has a progressive disease such as cancer or diabetes, and other therapeutic options existed that might have halted the progression.



Current FDA/ICH risk-benefit methodology calls for reviewers to distinguish adverse events that are attributable to progression of the underlying disease from adverse events that are caused by the drug itself. Only the latter harms are charged against a drug's risk-benefit ratio.³⁸ This has the effect of undercounting harms associated with badly targeted drugs, by failing to penalize them for avoidable progression of the underlying disease (i.e., progression that occurs in patients whose failure to respond might have been predicted through the use of a TAB test). If a patient loses his foot because he was taking a badly targeted diabetes drug to which he did not respond, that injury would be chalked up to “progression of the underlying disease” and not counted as a risk related to taking that particular drug. Ignoring these harms undercounts the true risks and societal costs of badly targeted drugs. Current methodology treats non-response as a factor that affects the denominator of the risk-benefit ratio, when in fact non-response may affect *both* the numerator and the denominator. Stated otherwise, current methodology models non-responders as receiving zero benefits and zero harms, when in fact there may be harms.

³⁷ “Lost-chance” doctrine, recognized in some U.S. states, allows injured patients to bring tort suits for injuries they have suffered as a result of progression of illness during a delay in diagnosis or negligent error in treatment. See, e.g., Martin J. McMahon, *Medical malpractice: Measure and Elements of Damages in Actions Based on Loss of Chance*, 81 A.L.R. 4th 485 (1990, as updated).

³⁸ HHS, FDA, *Reviewer Guidance: Conducting a Clinical Safety Review of a New Product Application and Preparing a Report on the Review* (Feb., 2005), at 5-6, 8, 12, 14; see, also, FDA, MAPP 6010.3, *supra* note 35, at 20 (§§ 7.1, 7.1.5.5).

This approach can mask incremental advantages associated with better targeting of existing drugs. Targeted therapies offer two potential advantages over traditional, “untargeted” drugs: 1) “safety pharmacogenomics” seeks to identify genetic factors that expose patients to a heightened risk of adverse drug reactions—i.e., injuries directly caused by ingestion of the drug—so that at-risk patients can be advised to avoid the drug; 2) “effectiveness pharmacogenomics” seeks to reduce the rate of treatment failure—i.e., to reduce the rate of non-response by screening out patients who would fail to derive therapeutic benefit from the drug. In practice, targeting strategies may achieve a combination of these two effects.

The current FDA/ICH risk-benefit methodology would accurately portray the advantages of a targeting strategy that works strictly by means of safety pharmacogenomics. Such a strategy reduces direct, drug-caused injuries of the type FDA/ICH methodology includes in the risk-benefit ratio. The targeted drug would display lower risks, and hence would have more attractive risk-benefit ratio, than the corresponding, untargeted version of the same drug. However, the FDA/ICH methodology displays only *some* of the advantages associated with effectiveness pharmacogenomics. As non-responding patients are screened out, a larger percentage of remaining patients who do take the drug will experience therapeutic benefits, so the targeted drug will display advantages in this respect. However, there is an additional advantage that the current methodology fails to capture: the targeted drug reduces lost-chance injuries caused by progression of the underlying disease in non-responders. These injuries were excluded from consideration, when calculating the risk-benefit ratio of the original, untargeted drug. The fact that the targeted version of the drug reduces those injuries would, therefore, not be visible as an advantage. The full merits of a better-targeted drug are systematically understated by the current methodology.

This approach may have been acceptable in the mid-twentieth century, when there was no way to predict which patients would or would not respond to a given drug. The phenomenon of non-response merits a more thorough analysis, to the degree that science now offers opportunities to target drugs in ways that could reduce these lost-chance injuries. How well a drug can be targeted is now a factor to be considered as part of its overall safety-and-effectiveness profile. The incremental safety and economic benefits of better targeted drugs cannot be appreciated, if regulators undercount the harms of badly targeted drugs. Precise targeting is a safety feature, akin to airbags in a car; regulatory decisions would be skewed if automotive safety statistics simply ignored the types of injuries that occur when cars lack airbags. The advent of targeted therapies calls for a rethinking of drug regulators’ old, pre-pharmacogenomic methodologies for assessing benefit and risk.

The example just given is simply that: a single example. Similar biases may exist in applying other common legal standards to TAB tests and targeted therapies. Such standards include: 1) regulatory standards for medical products and services, such as FDA’s standards for approving products and standards under the Clinical Laboratory Improvement Amendments of 1988 (CLIA)³⁹ for laboratory testing services; 2) reimbursement standards, such as “reasonable and necessary” concepts used in U.S. Medicare, Medicaid, and insurance reimbursement decisions and the cost-effectiveness standards other nations employ when deciding which treatments should be covered by their national health plans; and 3) standards of clinical care, patient protection, and tort liability, including state laws and court decisions on informed consent, medical practice standards, medical product liability, and physician malpractice in the use of

³⁹ Pub.L. 100-578, (Oct. 31, 1988), 102 Stat. 2903, *codified at* 42 U.S.C. § 263a *et seq.*; *see* regulations at 42 C.F.R. Pt. 493.

drugs. For all such standards, there is a need to evaluate how they apply in the specific context of targeted therapies and whether existing methodologies may bias day-to-day decisions by regulators, legislators, insurance administrators, healthcare providers, and product developers. Key questions are: 1) What are the specific problems in applying existing legal and regulatory standards to TAB tests and targeted therapies (e.g., are necessary data inputs unavailable, or does the methodology make assumptions that are questionable, in the case of a targeted therapy)? and 2) How can each such problem be addressed (e.g., by developing new regulatory guidance to clarify how an existing standard should be applied when analyzing a TAB test, by supplementing state informed consent statutes to address uncertainties, etc.)? Targeted therapies cannot achieve their full promise, if existing legal and regulatory standards are applied in ways that tend to mask their real advantages.

C. Coping with Uncertainty about the Benefits of TAB Testing

The incremental benefits of TAB testing and better-targeted therapies are, to some degree, unknowable—at least, they may not be discoverable through the clinical trials that have been the traditional basis for regulatory product approvals. The current shortcut of treating non-response to a drug as “zero benefit/zero harm” (see Section III.B *supra*) may simply reflect how devilishly hard it is to quantify the harms that flow from a patient’s use of an ineffective treatment. These injuries are consequential rather than direct. Estimating these injuries would require a comparison of probable health outcomes for alternative courses of treatment, or require prognostication of how patients’ illness may progress during a given period of non-response to a drug. Regulators have traditionally, and understandably, been hesitant to dwell on imponderable questions such as these. The issue, now, is whether appropriate regulation of targeted therapies will force these questions onto the regulatory agenda. The answer is, “Not necessarily.” Regulators cannot be expected to answer questions that, inherently, have no clear answers. However, if that is the case, our laws and regulatory policies may need to be adjusted to make allowance for the fact that the decisions regulators make about targeted therapies will be prone to considerable error and uncertainty. Uncertainty itself is not a problem, so long as appropriate allowances are made for the fact of that uncertainty. Coping with uncertainty may be the defining regulatory challenge of the pharmacogenomic era.

The incremental benefit of a targeted therapy depends on extrinsic factors, e.g., information about drugs other than the one that is under review, the nature of the patient’s medical condition, and how it may progress if not successfully treated. If no alternative therapies are available, then arguably there is no harm in trying an ineffective drug, other than the economic waste. If the patient’s condition is non-progressive, then trying an ineffective treatment produces no permanent injury, although it may cause prolongation of suffering (e.g., a codeine non-metabolizing patient suffers ongoing pain until switching to another drug, which then stops the pain). The harm non-responders suffer also depends on how long it takes to detect the lack of response (e.g., is it necessary to wait until cancer returns to infer that a treatment has been ineffective, or are there surrogate biomarkers of effectiveness that would let this conclusion be drawn earlier?).

In approving new drugs, FDA currently considers some of these extrinsic factors, including the presence and adequacy of alternative treatments and the seriousness and outcome of the disease that is being treated.⁴⁰ Such factors play into a qualitative

⁴⁰ HHS, FDA, *Statement Regarding the Demonstrations of Effectiveness of Human Drug Products*, 60 Fed. Reg. 39,180 (Aug. 1, 1995).

assessment, by FDA's reviewers and Advisory Committees, of the overall acceptability of a drug's risk-benefit ratio, but FDA is not required to conduct a comprehensive, systematic, or quantitative analysis of these factors. A more systematic and transparent decision algorithm may be needed in the case of targeted therapies, to ensure that the incremental advantages of various targeting strategies are adequately considered in FDA's decisions; to promote better public understanding of the fact that individual treatment response may be quite variable; to ensure that the interests of various subgroups of patients (responders, non-responders, and adverse responders) are treated even-handedly as FDA balances risks to some patients against benefits to others; to ensure that no genetically defined subgroup of patients is having its interests systematically and repeatedly neglected by drug developers or FDA; and to ensure that similar factors are being weighed in a consistent manner when approving similarly situated products.

Accepting how difficult it may be to estimate the lost-chance injuries that non-responding patients suffer, available regulatory resources may need to be focused on products where this risk of harm is highest. One possible approach would be to use a risk-stratification algorithm to help identify situations where a cautious analysis is most warranted. For each drug under review, this might mean compiling a chart in the form of Figure 2, *supra*, showing the frequency of beneficial response, non-response, and adverse response to the drug. For drugs with significant rates of non-response, regulators might then estimate the probability that non-response could actually cause serious, preventable injuries. This probability would depend on many factors, and the factors may differ for different classes of drug. Examples of the factors might include: 1) whether the condition being treated is progressive or non-progressive in nature; 2) how serious are the potential consequences of non-response to the drug (e.g., suicide in a non-responding depression patient, vs. prolonging a patient's cold for three additional days); 3) whether alternative therapies exist, such that non-responding patients would actually be foregoing other therapeutic options during treatment with the drug that is under review; 4) whether timely detection of non-response and adverse response is possible; 5) whether good options are available for mitigating the injuries that may result from non-response or adverse response to the drug; and 6) whether the drug will be used in a population that would have difficulty communicating non-response (e.g., infants or speech-impaired patients who would be unable to express that a pain medication is not working).

A risk-stratification algorithm of this sort can improve the quality of regulatory decisions, even if aspects of the analysis must remain qualitative and uncertain. Getting this algorithm right will be a key challenge drug regulators may face in an era of targeted therapies. At issue is whether a badly targeted therapy should be approved "as is," or are the risks to non-responders so serious that approval should be deferred until a better targeting strategy is identified. The decision either way has major commercial and public-health consequences. A countervailing concern is that requiring drugs to be targeted too precisely may delay or deny therapeutic benefits to many patients who could safely ingest a drug, to protect a narrow subgroup that is particularly susceptible to injury.

FDA is now entering a difficult decisional terrain where its approval decisions may entail interpersonal trade-offs among respective subgroups of its statutorily protected class, i.e., patients. Pharmacogenomics upends the simplifying assumption that all patients have an equal *ex ante* probability of enjoying a benefit or suffering

harm from a given drug. Drug-approval decisions in the era of targeted therapies pit the interests of various patient subgroups directly against one another. People whose livers are endowed with good genetic machinery for manufacturing drug-metabolizing enzymes may press for rapid approval of drugs that threaten to kill persons not so blessed. Other federal agencies, e.g., the Environmental Protection Agency (EPA) and the Federal Energy Regulatory Commission (FERC), have previously had to occupy this difficult terrain, where an agency's decisions may visit disparate impacts within the broader public it is seeking to protect. Industrial and residential electricity consumers may be differentially affected by a FERC rate-approval decision; so may FDA confront difficult conflicts within the larger class of drug-consuming patients. A possible trend to watch is whether, in this climate, FDA's decisions (and its decisional algorithms) may become subject to as much scholarly critique and judicial review as has been characteristic of EPA and FERC decisions in earlier years. Pharmacogenomics fractures the public into differently situated subclasses, and a divided public sharpens regulatory decisionmaking.

Despite efforts to improve FDA's methodologies for assessing the clinical benefits of targeted therapies, there will be a certain amount of ongoing, irresolvable uncertainty about the incremental benefits TAB tests and targeted therapies provide. The impact of this uncertainty, and the appropriate policy response to it, both are poorly understood at present: 1) how may uncertainty about the clinical utility of targeted therapies skew decisions by regulators, insurers, and courts? and 2) are there appropriate ways to mitigate these biases? For example, if the benefits of TAB testing cannot be accurately assessed, it may be appropriate to adjust tort liability standards so that physicians are not held to a higher standard of care than can be factually supported. If current drug and reimbursement approvals are biased in favor of badly targeted therapies, then offsetting policies may be needed, to level the playing field and promote timely clinical introduction of better targeted drugs. Such policies could include: special incentives to spur the development, reimbursement, and use of targeted therapies; expedited regulatory approval pathways to speed approval of targeted therapies that combine drugs and TAB tests; or reduced FDA evidentiary requirements for initial approval of TAB tests and targeted therapies, subject to postmarket study requirements to clarify uncertainty.

Rough estimation techniques may be able to provide partial information about the benefits of TAB testing, even when full estimation is impossible. These techniques might harness postmarket drug-safety data and clinical outcomes data to give a better sense of the harms that flow from badly targeted drugs. All who have an interest in accurate regulatory information will benefit from frank, transparent recognition of the biases that may exist, when information is imperfect. Potential beneficiaries include policymakers, regulators, healthcare providers, insurers, juries, and, in particular, physicians and patients who need to understand limitations of the regulatory processes on which they are relying for protection.

IV. REGULATORY APPROVAL OF TAB TESTS

A. The Current Regulatory Approval Status of TAB Tests and Issues with Adverse Event Reporting and Informed Consent

An important concern with TAB tests, as with all other genetic tests, is to protect patients from unreliable tests and excessive claims about what the tests can do. There is broad consensus about the need for some form of regulatory review to substanti-

ate claims that will be made about a genetic test, before allowing its use in clinical settings.⁴¹ Many genetic tests now in use have not been through this sort of review process—a fact of which many patients, and some physicians, are unaware. The United States has pursued a bifurcated policy that requires regulatory review of safety and effectiveness for some, but not all, genetic and diagnostic tests.

This situation reflects longstanding differences in the regulation of test products and testing services. FDA regulates *in vitro* diagnostic (IVD) devices, or test kits, that medical device manufacturers make for sale to clinical laboratories. These test kits, with limited exceptions, must pass through FDA's premarket clearance or approval processes, which require information to support analytical and clinical claims (if clinical claims are being made). An example of an analytical claim would be that a test detects a biomarker and does so with specified rates of false positives and negatives. Clinical claims could be that this biomarker is a valid indicator of a particular health condition (e.g., whether the patient is able to metabolize a particular drug, or whether the patient has a particular type of cancer) or that the test has utility in clinical care (e.g., to screen patients to reduce injuries from a specific drug). FDA requires substantiation before a TAB test kit can be marketed with these types of claims.

On the other hand, tests made in-house at clinical laboratories, colloquially known as “home-brew” tests, are regulated under CLIA.⁴² Home-brew tests traditionally have not had to pass through an external regulatory review process to substantiate claims, although they generally do receive internal validation by the labs that made them. A lab cannot sell its home-brew tests for use by others but can use them itself to provide testing services to the public. There recently have been calls to enhance CLIA regulation by adding a genetic testing specialty in which labs could qualify.⁴³ However, this would not alter the basic fact that CLIA has no mechanism for external regulatory review of home-brew tests.

In principle, FDA has the authority to require data demonstrating the safety and effectiveness of home-brew tests. However, FDA has, in recent years, declined to do so in an exercise of its enforcement discretion.⁴⁴ In September 2006, FDA issued draft guidance indicating that one type of home-brew tests, *in vitro* diagnostic multivariate index assays (IVDMIAs), must meet pre- and postmarket device requirements under the FDCA and FDA regulations, including, when applicable, premarket review

⁴¹ Francis S. Collins & Alan E. Guttmacher, *Genetics Moves Into the Medical Mainstream*, 286 JAMA 2322 (2001); David Melzer, Don Detmer & Ron Zimmern, *Pharmacogenetics and Public Policy: Expert Views In Europe and North America*, 4 PHARMACOGENETICS 689 (2003); David Melzer, Ron L. Zimmern, Don E. Detmer & Tom Ling, *Regulatory Options for Pharmacogenetics*, 4 PHARMACOGENOMICS 527 (2003).

⁴² See *supra* note 39.

⁴³ HHS, Centers for Disease Control & Prevention (CDC), *Notice of Intent; Genetic Testing Under the Clinical Laboratory Improvement Amendments*, 65 Fed. Reg. 25,928 (May 4, 2000); Genetic Alliance, *Genetic Alliance Calls for Genetic Testing Specialty Under CLIA* (Mar. 2, 2005), at http://www.geneticalliance.org/ws_display.asp?filter=clia_release; Juli Murphy, Gail Javitt, & Kathy Hudson, *Creating a Genetic Testing Specialty Under CLIA: What Are We Waiting For?* (Johns Hopkins University, Genetics and Public Policy Center, 2005), at <http://www.dnapolicy.org/policy/regulations/McClellanpaper.pdf>.

⁴⁴ See Steven Gutman, *Clinical Chemistry Forum: The Role of Food and Drug Administration Regulation of In Vitro Diagnostic Devices—Applications to Genetics*, 45 CLINICAL CHEMISTRY 746 (1999); HHS, FDA, *Final Rule, Medical Devices; Classification/Reclassification; Restricted Devices; Analyte Specific Reagents*, 62 Fed. Reg. 62,243, 62,249 (Nov. 21, 1997). See, also, Richard D. Schifreen & Cynthia Louth, *Industry View on the Regulation of Ancillary Reagents*, 51 FOOD & DRUG L.J. 155, 159 (1996).

requirements for class II and III devices.⁴⁵ IVDMIAs typically employ complex mathematical algorithms, often with the aid of computer software, to interpret large amounts of genetic or protein data to yield results that can be used to guide medical decisionmaking.⁴⁶ These tests include some of the complex genetic and proteomic tests, such as tests that analyze breast-tumor genes to assess whether a particular patient might benefit from chemotherapy, that are expected to play an important role in personalized medicine.⁴⁷ However, many TAB tests do not fall within the definition of an IVDMIA. The recent draft guidance is one discrete step toward enhanced FDA oversight of home-brew tests.

There have been calls for FDA to assume an even greater role in oversight of home-brew genetic tests. In 1997, a joint National Institutes of Health (NIH)—Department of Energy (DOE) task force recommended systematic, well-designed studies to assess the safety and effectiveness of genetic tests before they become routinely available and after they undergo significant modifications.⁴⁸ Three years later, the Secretary's Advisory Committee on Genetic Testing (SACGT) called for FDA to assume responsibility for premarket review, approval, and labeling of all new genetic tests that have moved beyond the basic research stage.⁴⁹ SACGT envisioned data-driven reviews focusing on the analytical and clinical validity of genetic tests, as well as on any claims the developer plans to make about a test's clinical utility.⁵⁰ Despite these recommendations, it is likely that many types of CLIA- and FDA-regulated tests will remain subject to different approval standards for the immediately foreseeable future.

Debate about appropriate reforms in this area has been clouded by lack of good, basic data clarifying the number of home-brew TAB tests available and the potential risks they pose. The scant data that are available tend to reflect diagnostic testing or genetic testing in general, with very little information specifically addressing TAB tests used in targeting of therapies (Box 1). Information about FDA-approved TAB tests is readily available, but there is no single, good source of data on how many CLIA-regulated TAB tests are offered and how widely they are being used in clinical decisionmaking. Grant-making entities such as the NIH should consider funding empirical studies of these matters. Potential sources of data could include physician surveys, surveys of clinical laboratories, and even insurance claims data. There is also a need for improved public disclosure of the internal review processes clinical laboratories use in validating home-brew TAB tests. CLIA-regulated tests receive some form of internal review by the labs that developed them; however, details often are treated as confidential business information, making it hard to judge how rigorous these review procedures are. Without more information, it is difficult to assess

⁴⁵ HHS, FDA, *Draft Guidance for Industry, Clinical Laboratories, and FDA Staff on In Vitro Diagnostic Multivariate Index Assays* [Docket No. 2006D-0347] (Sept. 5, 2006), at www.fda.gov/OHRMS/DOCKETS/98fr/ch0641.pdf.

⁴⁶ FDA, *FDA Drafts Regulatory Guidance to Industry and Labs for Group of Medical Tests*, (News release P06-127, (Sept. 5, 2006)), at <http://www.fda.gov/bbs/topics/NEWS/2006/NEW01445.html>.

⁴⁷ Andrew Pollack, *F.D.A. Seeks to Regulate New Types of Diagnostic Tests*, THE NY TIMES, n.p. (Sept. 6, 2006).

⁴⁸ NIH—DOE Task Force on Genetic Testing, *supra* note 5, at ch. 2.

⁴⁹ NIH, SACGT, *supra* note 5, see Executive Summary at x.

⁵⁰ *Id.* at x, 15—20.

how serious should be the concern about the clinical use of home-brew TAB tests to direct patient care.

Box 1: Regulatory Approval Status of Currently Available Tests

Data on Genetic Tests of All Types. Data for the year 2000 indicated that at least 301 clinical or research genetic tests were offered in the U.S.,⁵² with 158 laboratories offering clinical tests;⁵³ however, only six specific genetic tests had been cleared or approved by FDA.⁵⁴ These figures refer not only to TAB tests, but to genetic tests of all types, such as tests for mutations in the BRCA1 and BRCA2 genes. BRCA tests are widely used to predict patients' future risk of breast and ovarian cancer, even though no BRCA test has ever been approved by FDA.⁵⁵ As of 2003, an NIH-contracted resource for genetic tests was reportedly offering more than 1,000 genetic tests, of which only 6 had been brought before FDA for approval.⁵⁶ A 2003 survey of U.S. molecular diagnostics laboratories found that genetic testing was their second-largest activity, after infectious disease testing, in terms of the volume of molecular diagnostics tests they performed; 85 percent of the labs surveyed reported using at least one home-brew test.⁵⁷

Data on TAB Tests. In the subgroup of TAB tests, only a handful of FDA-reviewed tests now exists. For example, in 1998, FDA approved the first molecular diagnostic test for use in detecting the HER-2 protein, which is the target for the breast-cancer biologic therapy, trastuzumab (Herceptin™), and FDA has subsequently approved a test for this protein based on FISH technology. FDA also has cleared a test for genetic variations in HIV virus, for use in selecting appropriate therapies. It was not until December, 2004 that FDA cleared a drug-metabolizing enzyme genotyping system, designed for use in detecting a patient's cytochrome P450 genotype.⁵⁸ In August, 2005, FDA cleared a second test of this type, for use in detecting variations in the UGT1A1 gene that encodes the enzyme UDP-glucuronosyltransferase, which affects metabolism of irinotecan. The arsenal of FDA-reviewed TAB tests is still quite small.

In addition to having no mechanism for external review of the validity and utility of tests, CLIA also lacks the postmarket vigilance and adverse-event reporting mechanisms that FDA's regulations provide.⁵⁸ To date, there have been few documented cases where

⁵¹ ADVAMED SUBMISSIONS WORKSHOP (July 18, 2000); see, Presentation of D.W. Feigal, Jr., Center for Devices and Radiological Health (CDRH), *Future Trends*, at: <http://www.fda.gov/cdrh/present/hima-7-19-00-feigal.pdf>. See SI. 21—23.

⁵² *Id.*

⁵³ *Id.*

⁵⁴ National Academy of Sciences, National Cancer Policy Board, Board on Science, Technology, and Economic Policy, *SAVING WOMEN'S LIVES: STRATEGIES FOR IMPROVING BREAST CANCER DETECTION AND DIAGNOSIS* 225 (2005), at <http://www.nap.edu/catalog/11016.html>.

⁵⁵ *Id.*

⁵⁶ Enterprise Analysis Corporation, *Molecular Diagnostics—An In-depth Survey of the U.S. Molecular Diagnostic Laboratories* (Nov. 2003), at <http://www.researchandmarkets.com/reports/310296>.

⁵⁷ FDA, *FDA Clears First of Kind Genetic Lab Test* (News release PO4-111, (Dec. 23, 2004)).

⁵⁸ 21 CFR 806 (providing for reporting of corrective changes made in medical devices and removals of devices from the market); 21 CFR 803 (establishing requirements for medical device reporting).

patients experienced harm because of errors in a CLIA-regulated genetic test.⁵⁹ However, the lack of reports gives little comfort, in the absence of any reporting requirement. Appropriate reporting systems need to be developed for adverse events associated with the clinical use of CLIA-regulated TAB tests, even if other issues with CLIA regulation are deferred for later resolution. Key questions are: 1) what should constitute a reportable adverse event in the context of TAB testing and targeted therapies? and 2) what are the most workable mechanisms for reporting these events? The latter mechanisms might include voluntary reporting by physicians or more formal reporting requirements for physicians and/or clinical laboratories.

Only rarely will the test itself cause patient injury; in many cases, testing requires only a minimally invasive blood draw or sampling of tissue. Yet patients may suffer serious adverse reactions to drugs they take based on inaccurate test results (or test results that are accurate, but erroneously understood and applied by the clinician). Lack of effectiveness in a TAB test becomes a safety problem in its own right, if it translates into serious or fatal drug-related injuries. The question is how these injuries should be reported—as a drug-related event, as a test-related event, or both. It is difficult, with a targeted therapy, to distinguish whether an adverse event was caused by the drug or by the (mis)targeting of the drug. Accepting that this difficulty will always exist, a consistent approach to reporting is crucial. If some of these events are attributed to the drug, while others are attributed to problems with a test or in the use of test results, it will not be possible to assemble a true picture of why patients are being injured and whether such injuries could be prevented through better use of existing test procedures. The objective should be to bring data about FDA- and CLIA-regulated TAB tests together with data about the drugs they target and the clinical outcomes these drugs produce, so that there is a single source of useful information to guide clinicians in day-to-day decisions to order tests and prescribe medicines. For drugs with known or suspected genetic variability of patient response, adverse-event reports may need to include information about whether a TAB test was performed at all and, if so, which specific test was used; what the test result was; and whether the clinician's decision to prescribe the drug was in line with the current understanding of which drugs are appropriate for patients with similar test results. This level of detail is needed to support future improvements in drug targeting: e.g., are injuries traced to a failure to use available tests; are injuries higher with one test as opposed to another; do there appear to be problems in defining the range of test results that corresponds to a patient's having a good response to a drug; or is the problem that clinicians are taking inappropriate actions in response to test results? How to fix the problems depends on what the problems are, and it is essential to develop reporting mechanisms that capture the needed information.

Home-brew TAB tests also may present informed consent issues. The laws of all U.S. states require informed consent for medical therapy, but not all states clearly require informed consent to the use of diagnostic tests.⁶⁰ However, TAB tests have a very direct influence on therapeutic decisions, and the validity of a patient's consent to medical therapy becomes questionable, if that consent was ill informed by faulty TAB testing. Uncertainties inherent in TAB testing arguably need to be disclosed as part of the *treatment* consent, even if state law does not require a separate *diagnostic* consent to the test itself. In particular, patients may regard it as material and want to know whether they are basing important treatment decisions on a TAB test that has never been reviewed by an external regulator. TAB testing is serious business with serious medical consequences.

⁵⁹ E.g., a lawsuit settled out of court, after several children were born with Tay-Sachs disease after their parents were erroneously characterized by a home-brew carrier-screening test.

⁶⁰ W.J. Curran, M.A. Hall, M.A. Bobinski, D. Orentlicher, *HEALTH CARE LAW AND ETHICS* (5th ed., 1998), at 234-235 (noting that state informed consent statutes are not always clear whether disclosure of diagnostic alternatives, as opposed to treatment alternatives, is required).

A patient may be denied life-saving cancer therapy based on a TAB test that indicates the patient is not a suitable candidate for a targeted cancer drug. A patient may receive a drug that has lethal side effects, if a TAB test erroneously indicates that the patient will be a good metabolizer of that drug.

State informed consent statutes need to clarify situations in which TAB testing should be addressed as part of the medical treatment consent discussion. These situations could include those where a patient is making treatment decisions about a serious or life-threatening disease or is facing treatment with a drug that is known to produce serious side effects in some patients. Possible approaches, in these situations, might be: 1) to inform the patient whether TAB tests exist that may aid in the selection of drugs for treating their condition or in reducing the rate of adverse events associated with those drugs; 2) to inform the patient whether available TAB tests have received external regulatory review; and 3) if the available tests have not received external regulatory review, to inform the patient about possible uncertainty of test results and the available options for addressing that uncertainty (e.g., confirm test results using another available TAB test, adjust the initial drug dosage until the patient's response can be assessed, monitor the patient to ensure early detection of adverse reactions, etc.).

The modern trend among states is toward a patient-centered standard of disclosure (i.e., information should be disclosed if patients would regard it as material to their decisions)⁶¹ and this trend also is reflected in standards published by the American Medical Association⁶² and Joint Commission on Accreditation of Healthcare Organizations.⁶³ At the federal level, FDA requires that the non-approved status of a home-brew test be disclosed to physicians, in cases where the test incorporates an FDA-regulated analyte-specific reagent.⁶⁴ However, home-brew tests that were made with other chemicals require no such disclosure. This creates an ironic situation where tests that have had the least amount of FDA scrutiny are subject to the lowest disclosure requirements. Empirical studies are needed, to assess whether patients and physicians are ill informed about the regulatory approval status of home-brew tests, and whether patients regard this as

Figure 3
FDA Review of Genetic Tests

Scope of Coverage ↓	Intensity of Review →		
	Analytical Claims	Claims of Clinical Validity	Claims of Clinical Utility
IVD Products	✓	✓	✓
Home-brew Tests			

⁶¹ See, e.g., Curran *et al.*, *Id.* at 217-221; Canterbury v. Spence, 464 F.2d 772 (D.C. Cir. 1972); P.H. Schuck, *Rethinking Informed Consent*, 103 YALE LAW J. 889, 900-905 (1994).

⁶² AMA, E-8.08 INFORMED CONSENT, at <http://www.ama-assn.org/ama/pub/category/print8488.html>.

⁶³ JCAHO, COMPREHENSIVE ACCREDITATION MANUAL FOR HOSPITALS: THE OFFICIAL HANDBOOK (AUG. 3, 2004), Standard RI.2.40, *Elements of Performance for RI.2.40*, at p. RI-11.

⁶⁴ 21 CFR §§ 809.10(e)(1)(x),(xi); 809.30(c),(d)(2),(d)(3),(e).

a material factor about which they would wish to be informed when making decisions about the use of targeted therapies.

B. Optimizing Regulatory Review of TAB Tests: The Problem of Distinguishing Regulation of Medical Products from Regulation of Medical Practice

To address the disparity in review requirements for FDA- and CLIA-regulated tests, two key variables can be adjusted: a) the intensity of review (i.e., how many aspects of test performance must be externally substantiated before a test is allowed in clinical use?), and b) the scope of regulatory coverage (i.e., how many and what types of tests will be subjected to this review process?).

Figure 3 is a schematic of current U.S. policy on premarket review of genetic tests. FDA-regulated *in vitro* diagnostic products receive intense review to substantiate claims made about analytical validity, clinical validity, and clinical utility. (Refer to Section IV.A *supra* for examples of such claims.) However, regulatory coverage is limited, since CLIA-regulated tests are not generally subject to these same review requirements. SACGT's recommendations in 2000 called on FDA to assume responsibility for review, approval, and labeling of *all* genetic tests, with FDA's review focusing on analytical and clinical validity as well as on any claims the developer plans to make about a test's clinical utility.⁶⁵ This would amount to adding check marks across the bottom row of Figure 3, maintaining the current intensity of FDA review but expanding the regulatory coverage. The recent FDA draft guidance on IVDMIAs would achieve this effect for that particular class of home-brew tests.⁶⁶ SACGT's recommendations were controversial and, to date, have not been implemented. There are merits on either side of the issue. Subjecting home-brew tests to a more intensive review would promote a level playing field and perhaps promote greater investment in TAB-test research by FDA-regulated manufacturers. However, some in the industry are concerned that intensive FDA review of home-brew genetic tests could reduce the number and types of tests available, delay the clinical introduction of new tests, and increase costs.



One way to address these concerns would be to extend regulatory coverage to all tests, but reduce the intensity of FDA review for all tests. This is shown in Figure 4. Test kits and home-brew tests both would receive external regulatory review, but the review would concentrate on analytical validity and perhaps some, but not all, clinical claims. Remaining aspects of clinical validity and utility would be treated as medical practice issues, and oversight would come primarily from agencies that regulate medical practice or from within the medical profession itself. Admittedly, any proposal to reduce the intensity of FDA review seems controversial, at a time when FDA is under pressure to increase its oversight of safety issues after last year's problems with late-discovered risks in COX-2 painkillers. However, reducing the intensity of FDA review of genetic and diagnostic tests need not imply that the clinical utility of these tests would be left wholly unregulated. Rather, it would mean creating alternative institutional arrangements for validating the clinical utility of these tests.

⁶⁵ NIH, SACGT, *supra* note 5, at x, 15 – 20.

⁶⁶ FDA, *supra* note 45.

The approach shown in Figure 4 may be particularly appropriate in the context of TAB testing, even if it is not adopted for other types of genetic tests and *in vitro* diagnostic products more generally. TAB tests present difficult problems in drawing the line between regulation of medical products and regulation of medical practice. Because TAB tests are intended for use in directing treatment decisions, these tests have an immediate and inevitable linkage to the clinical practice of medicine. Bad TAB tests will not merely leave patients suffering social and psychological harms of being wrongly tagged with a stigmatizing genetic condition. Rather, bad tests may cause patients to receive drugs that will be toxic for them, or to be denied drugs that might have saved their lives. It is true, of course, that other types of genetic test also affect patient-care decisions: e.g., a positive genetic test for familial adenomatous polyposis may cause a patient to opt for more frequent colon-cancer screening. However, for TAB tests, the linkage to treatment decisions is prompt, consistent, and direct. Moreover, the safety and effectiveness of a TAB test may depend as much on how the test is applied in day-to-day clinical use, as on factors that can be assessed during premarket regulatory review. The fact that a patient has been tested with an FDA-reviewed genetic test is no guarantee that the test procedure has clinical validity or utility, if the test is being

Figure 4
Alternative Approach for TAB Tests

		Intensity of Review 		
Scope of Coverage 		Analytical Claims	Claims of Clinical Validity	Claims of Clinical Utility
	IVD Products	Product Regulation (FDA)	Divide Between Product & Practice Regulation	Regulate Primarily as Medical Practice Issues
	Home-brew Tests	Product Regulation (FDA)	Divide Between Product & Practice Regulation	Regulate Primarily as Medical Practice Issues

used for a purpose other than its FDA-approved indication. For example, a physician might order a test of a patient's cystic fibrosis gene carrier status, on the theory that this information has relevance in selecting an appropriate chemotherapy for the patient's colon cancer. Even if FDA has established that this test is valid in its intended use—i.e., to determine whether a person carries a copy of the cystic fibrosis gene for purposes of reproductive planning—the test would not necessarily have any clinical validity or utility in this off-label use. FDA traditionally has declined to restrict off-label uses of the products it approves.⁶⁷ Ensuring the clinical validity and utility of TAB tests may require tighter control of clinical applications than FDA traditionally has exerted in connection with its regulated products.

⁶⁷ Dep't of Health, Education & Welfare (HEW), FDA, *Legal Status of Approved Labeling for Prescription Drugs; Prescribing for Uses Unapproved by the Food and Drug Administration (Notice of Proposed Rulemaking)*, 37 Fed. Reg. 16,503-16,505 (July 30, 1972).

In carrying out its responsibilities under the FDCA, FDA has steered a careful course between regulation of medical products and regulation of medical practice. The legislative debate of the late 1930s, before passage of the FDCA, focused considerable attention on the proper scope of federal power to regulate medical practice, which had traditionally been a matter for state regulation.⁶⁸ Congress made clear that by passing the FDCA, it did not intend to authorize broad FDA regulation of the practice of medicine.⁶⁹ Courts have not found constitutional limits on FDA's power to regulate physicians,⁷⁰ but the agency, as a matter of policy, has sought to avoid direct regulation of their activities.⁷¹ For example, FDA has stated "labeling is not intended either to preclude the physician from using his best judgment in the interest of his patient, or to impose liability if he does not follow the package insert."⁷² Under this policy, FDA regulates the claims made by test developers but does not regulate the claims physicians make about a test. The problem with TAB tests is that these latter claims, quite often, are the key to the test's safety and effectiveness.

TAB tests pose a regulatory dilemma: their clinical utility may be indeterminate, without specifying in considerable detail how they will be used in the clinic. The question, then, is which regulator(s) should be responsible for overseeing the clinical utility of TAB tests? Before defining FDA's role with respect to this question, there needs to be a studied analysis of what the product/practice distinction *means* in the context of pharmacogenomics and personalized medicine. In particular, will ensuring the clinical utility of TAB tests require restrictions on off-label use that go beyond FDA's traditional policies on this matter? If so, effective oversight of the clinical utility of TAB tests by FDA could place the agency in a legally problematic role of regulating medical practice. Further, it may imply inflexible federal restrictions on off-label use of TAB tests that could deny patients the therapeutic benefits that many off-label uses do provide.⁷³ Is this what it will take and, if so, is this what we want?

Protecting the public from faulty targeting of medicines, while preserving the crucial distinction between product and practice regulation, may require careful sharing of oversight responsibilities among FDA, state medical boards, the scientific community, and the medical profession itself. Some of the genetic testing policy recommendations of the past decade, including those by SACGT, arguably would blur this distinction if the recommendations were applied to TAB tests. Appropriate regulatory structures for TAB tests must take account of special issues that arise because of the close linkage these tests have to clinical decisionmaking and because knowledge of how to target therapies is continuously and rapidly evolving. Traditional methods of incorporating scientific and medical advice into regulatory decisions may be too cumbersome or too slow to keep up. It ultimately may be necessary to develop new processes or even new regulatory institutions (formal or informal) to share in the work of validating TAB tests and targeted therapies.

⁶⁸ Joel E. Hoffman, *Administrative Procedures of the Food and Drug Administration*, in 2 FUNDAMENTALS OF LAW AND REGULATION: AN IN-DEPTH LOOK AT THERAPEUTIC PRODUCTS (David G. Adams, Richard M. Cooper & Jonathan S. Kahan eds., (1999)) at 17-24.

⁶⁹ HEW, FDA, *supra* note 67, 37 Fed. Reg. at 16,503-16,504.

⁷⁰ David G. Adams, *The Food and Drug Administration's Regulation of Health Care Professionals*, in 2 FUNDAMENTALS OF LAW AND REGULATION, *supra* note 68, at 423.

⁷¹ *Id.*, at 425-426, *see also* 37 Fed. Reg. at 16,503-16,504.

⁷² 37 Fed. Reg. at 16,504.

⁷³ David G. Adams, *supra* note 70, at 423; *see, also*, William L. Christopher, *Off-label Drug Prescription: Filling the Regulatory Vacuum*, 48 THE FOOD & DRUG L.J. 247 n.6 (1993).

Some of FDA's own recent approaches may offer useful models for sharing of responsibilities. An example is FDA's openness to the referencing of reliable, outside scientific sources to validate clinical claims for drug-metabolizing enzyme (DME) genotyping systems. This type of TAB tests assesses whether a patient carries genes for encoding specific enzymes needed to metabolize certain drugs. An example would be a test to determine which of many CYP-450 alleles a patient carries; this information is useful in targeting a number of different drugs. FDA has classified DME genotyping systems as Class II (moderate risk) devices that can be cleared through the 510(k) process.⁷⁴ For these test systems, FDA requires data on basic analytical factors (e.g., analytical sensitivity, assay limits, interference, repeatability, and reproducibility) and method comparison studies showing that the test detects the genotypes it claims to detect.⁷⁵ Clinical validity also must be substantiated; however, FDA has stated that it will not necessarily require prospective clinical studies, if there is an established scientific framework and a sufficient body of evidence supporting the clinical validity and utility of the device.⁷⁶ For enzymes where there are multiple, peer-reviewed studies that tested appropriate populations, these published studies can be used to substantiate clinical validity and utility of the test. If the literature does not adequately support the test's indications for use, clinical claims would generally need to be supported with prospective studies.⁷⁷

This approach, in effect, amounts to a sharing of responsibility for validation of these tests between FDA and an external authority—in this case, the scientific community by reference to peer-reviewed pharmacogenetics literature. While it certainly is not new for FDA to incorporate reliable, outside sources of data in its product-approval decisions, this overall approach may have broader application in the context of TAB tests. Clinicians need clear, current instructions on how to use TAB tests in targeting medicines, but the science of targeting is evolving so rapidly that it may be difficult for product labeling to stay current (*see* Section V *infra*). Another special problem is to strike an appropriate balance between product and practice regulation. Both these problems might be addressed by allowing FDA-approved labeling for TAB tests and targeted therapies to reference current TAB-testing guidelines maintained by an external TAB Clinical Standards Board. This Board would be formed within the medical and scientific communities to review the latest scientific evidence on TAB tests and maintain current guidelines for use of TAB testing in targeting particular medicines. Rather than having labeling include specific instructions for how to use a test to target a particular medicine (information that may rapidly grow out of date), FDA-approved labeling might simply state that the product is approved for use in accordance with current TAB-testing guidelines (as continuously updated by the TAB Clinical Standards Board). Reference to these external guidelines could reduce the need for frequent relabeling of products as targeting strategies improve and as clinical utility becomes better understood. Moreover, it would let the medical profession maintain a voice in aspects of product regulation that, in the case of targeted therapies, touch on medical practice.

Validation and labeling of TAB tests and targeted therapies will require innovative thinking and possible creation of new institutions, such as the TAB Clinical Standards

⁷⁴ 21 CFR 862.3360 (Classification regulation for drug metabolizing enzyme genotyping system).

⁷⁵ HHS, FDA, *Guidance for Industry and FDA Staff: Class II Special Controls Guidance Document: Drug Metabolizing Enzyme Genotyping System* (Mar. 10, 2005), at 12.

⁷⁶ *Id.* at 13.

⁷⁷ *Id.* at 14.

Board just described. A useful first step would be to convene workshops to elicit views of concerned constituencies, including members of the medical profession and scientific communities, state medical practice regulators, federal regulators charged with oversight of medical products and clinical laboratory services, patient advocacy groups, health insurers and payers, drug and device manufacturers, and the clinical laboratories industry. These workshops should seek consensus on the following issues: 1) the appropriate scope and intensity of FDA's review activities for TAB tests; 2) where to draw the line between product and practice regulation for TAB tests; and 3) what are the options for oversight of medical practice issues that affect the safety and effectiveness of TAB tests. Concerning this third issue, various approaches are possible, e.g., to rely on voluntary educational efforts within the medical profession; to involve state medical boards in regulating the clinical use of TAB tests and targeted therapies; or to create altogether new institutions such as a TAB Clinical Standards Board. Some efforts are already underway to address medical practice issues with TAB testing,⁷⁸ but this matter is far from resolved. Statutory and regulatory amendments may ultimately be needed, to achieve a workable division of product and practice regulation for targeted therapies.

C. Phased Approval Strategies for TAB Tests and Targeted Therapies

A phased approval process may offer advantages as a way to let drugs move to market promptly, subject to ongoing efforts to improve their targeting in the postmarket period. The essential feature of phased approach is that it confers some, but not all, of the advantages ordinarily associated with a drug approval when the drug is initially approved, but grants other advantages only if the manufacturer performs specific duties after the initial approval. FDA's existing accelerated approval process for drugs that treat serious, life-threatening conditions bears features of a phased approach. Accelerated approval can be granted, subject to special conditions of use or duties to conduct postmarket studies to confirm the drug's effectiveness.⁷⁹ In recent years, there have been various proposals to adopt phased approval for all drugs⁸⁰ and for the types of tests used in targeting drugs, i.e., genetic tests,⁸¹ and other *in vitro* diagnostic products.⁸²

⁷⁸ See, e.g., David Gurwitz, Abraham Weizman & Moshe Rehavi, *Education: Teaching Pharmacogenomics to Prepare Future Physicians and Researchers for Personalized Medicine*, 24 TRENDS IN PHARMACOLOGICAL SCIENCES 122 (2003); A. Woelderink, D. Ibarreta, M.M. Hopkins & E. Rodriguez-Cerezo, *The Current Clinical Practice of Pharmacogenetic Testing in Europe: TPMT and HER2 as Case Studies*, 6 THE PHARMACOGENETICS J. 3 (2006).

⁷⁹ 21 C.F.R. § 314.510.

⁸⁰ R.L. Woosley & G. Rice, *A new system for moving drugs to the Market*, ISSUES IN SCIENCE & TECHNOLOGY ONLINE (Winter 2005), at <http://www.issues.org/issues/21.2/woosley.html> (calling for phased approval of drugs).

⁸¹ See NIH—DOE Task Force on Genetic Testing, *supra* note 5, at Ch. 2 (discussing the possibility of granting conditional approval of genetic tests in cases where ongoing data collection is needed to confirm clinical validity and utility. Such tests could be marketed, covered by insurance, and promoted subject to disclosure that safety and effectiveness are still under investigation).

⁸² B.M. Thompson, *The IVAT [In vitro analytic test] Solution*, IVD TECHNOLOGY (Mar., 2004) (discussing a phased approval process for *in vitro* diagnostic tests, allowing tests with known analytical validity to be marketed, subject to ongoing data collection to confirm clinical validity and utility, and with restrictions on clinical claims that the manufacturer could make). See, also, G.F. Freiberg, *Deregulating the clinical utility of IVD products*, IVD TECHNOLOGY (Mar., 2006) (discussing strategies to resolve the discrepancy between home-brew and FDA-regulated genetic tests, including adjusting the intensity of review and phasing the review of analytical and clinical claims).

A traditional, non-phased approval can be viewed as a point-in-time event, which confers an entire package of rights, duties, and commercial advantages on the product's manufacturer. For example, once a drug is approved, it can be sold widely and its manufacturer can advertise and promote it for specified clinical purposes. An approved drug can be prescribed off-label by physicians and may enjoy increased sales as a result, even though the manufacturer cannot promote these uses.⁸³ Once approved, the drug can be prescribed without having to follow the cumbersome informed consent and human-subject protection requirements that apply during its investigational phase.⁸⁴ Investigational drugs may be able to obtain insurance and Medicare reimbursement, but reimbursement obviously becomes much easier once a drug is approved and is no longer seen as experimental. There are, of course, duties that come with a drug's approval. FDA regulations impose various new inspection, monitoring, and reporting requirements⁸⁵ that come into effect after a drug is approved, although some of these are only voluntary in nature.⁸⁶ Manufacturers have only limited duties to conduct further studies of the safety and effectiveness of approved drugs. Traditionally, FDA lacked a clear statutory mandate to require postmarket study of drugs,⁸⁷ although the agency claimed it could require such studies as part of FDA's general powers to enforce the FDCA and to require drug companies to provide data bearing on whether previously granted approvals should be withdrawn.⁸⁸ The 1992 accelerated approval program, for drugs that treat serious or life-threatening diseases, clearly authorized FDA to require postmarket studies of effectiveness (to confirm the relation of surrogate endpoints to actual clinical benefits),⁸⁹ but not of safety. Recent data suggest that completion rates, even for these limited postmarket study requirements, have been poor.⁹⁰

A phased approach would let new drugs enter the market with some, but not all, of the commercial advantages just discussed, and manufacturers might face some additional duties. There might be initial restrictions on advertising and promotion, postmarket study requirements, or enhanced requirements to monitor and report adverse events. These special conditions would cease, if the drug later met agreed targets for safety and effectiveness in actual clinical use.

While a phased approach may not be appropriate for all new drugs, it could have real merit for drugs that appear, after Phase III clinical trials, to be poorly targeted. These would be drugs that offer clear therapeutic benefits for some patients, while producing high rates of non-response or serious adverse events in other patients, with the variability still unexplained at the time the drug is initially approved. New targeting strategies may continue to be discovered after such drugs are approved (*See* Section II, *supra*, at Scenario III), leading to fundamental improvements in their risk-benefit ratios. A phased strategy would let a manufacturer's rights and duties be adjusted as better targeting improves a drug's risk-benefit ratio over time. For example, initial approval could be granted, subject to a requirement to conduct postmarket pharmacogenetic

⁸³ 37 Fed. Reg. 16,503-16,505 (June 30, 1972).

⁸⁴ 21 C.F.R. Parts 50, 56.

⁸⁵ 21 C.F.R. § 314.80-81.

⁸⁶ Alastair J.J. Wood, C. Michael Stein, & Raymond Woosley, *Making Medicines Safer—The Need for an Independent Drug Safety Board*, 339 N. ENG. J. MED. 1851 (1998).

⁸⁷ *See, e.g., FDA's Drug Approval Process: Up to the Challenge?*, Hearing Before the S. Comm. on Health, Education, Labor & Pensions, 109th Cong., 1st Sess. (Mar. 3, 2005), statement of William B. Schultz, Partner, Zuckerman Spaeder LLP, at http://help.senate.gov/Hearings/2005_03_01/schultz.pdf.

⁸⁸ 21 U.S.C. §§ 371(a), 355(k) (FDCA §§ 701(a), 505(k)); *see also* Geoffrey Levitt, James N. Czaban & Andrea Patterson, *Human Drug Regulation*, in 2 FUNDAMENTALS OF LAW AND REGULATION, *supra* note 68, at 179.

⁸⁹ 21 C.F.R. § 314.510.

⁹⁰ Susan Okie, *What Ails the FDA?*, 352 N. ENG. J. MED. 1063 (2005).

studies to clarify why patients vary in their response to the drug. Specific objectives could be set to reduce the rate of adverse events and non-response within a set period of time, e.g., five years. Poorly targeted drugs might be placed under special disclosure requirements, to make sure patients are aware of a drug's low rate of therapeutic success. Such disclosures could be made through special labeling, through mandatory disclosure of non-response rates in advertising, or, in the case of serious adverse events, through special informed-consent requirements to be administered by the clinician at the point when the drug is prescribed. These disclosure requirements could be eased over time as the drug became better targeted, as proved by actual clinical outcomes data. Phased approval of poorly targeted drugs, obviously, may require changes in FDA's existing statutory authority. The science of drug targeting has matured to a point where it now may make sense to consider these changes. Phased approval for badly targeted drugs would give drug manufacturers clearer incentives to conduct postmarket studies to improve the targeting of their products—an incentive that is very weak under current statutes and regulations.⁹¹

A phased process also may make sense for clearance or approval of new TAB tests. The clinical utility of a new test often cannot be fully evaluated until the test is in wide clinical use.⁹² This is especially true in the case of TAB tests, where clinical utility is measured in terms of improved clinical decisionmaking. A phased strategy would let new TAB tests enter the market subject to restrictions. For example, new TAB tests might be granted initial clearance based on proof of their analytical validity, with postmarket study requirements to substantiate their clinical validity and utility for use in targeting particular drugs. After this first approval, the TAB test could be marketed for clinical use, subject to informed consent or disclosure requirements, so that patients would know that the test's clinical validity and utility are not yet fully established. Efforts could be made to promote insurance coverage for TAB tests following their initial clearance. This could be similar in concept to the proposed Medicare coverage-with-evidence-development policy, which would allow experimental therapies to receive Medicare reimbursement subject to ongoing data-collection requirements. TAB tests could be required to obtain a second, final regulatory clearance at a later date, after their clinical claims have been further substantiated. To create an incentive to complete the postmarket studies, TAB tests could be required to gain this second clearance in a fixed period of time (e.g., five years) or else be withdrawn.

In the era of pharmacogenomics, drug approval decisions involve explicit interpersonal trade-offs among subgroups of patients who benefit, fail to respond, or are harmed by a particular drug. Phased approval offers opportunities to balance the interests of these respective groups by letting promising new therapies reach benefiting patients promptly, while requiring ongoing efforts to protect the adverse- and non-responders. Phased strategies appear particularly appropriate for 1) new TAB tests, in cases where clinical utility remains uncertain, and 2) new drugs that are poorly targeted at the time of their initial approval (i.e., drugs for which premarket clinical trial data show substantial rates of unexplained patient non-response or adverse response). Policymakers should evaluate the merits of various phased approval approaches and consider specific amendments to the FDCA, FDA regulations, CLIA, Medicare/Medicaid reimbursement policies, and state insurance regulations to support phased approval of poorly targeted drugs and the tests that are needed to target these drugs more precisely.

⁹¹ See, generally, Evans *et al.*, *supra* note 3.

⁹² National Academy of Sciences, *supra* note 54.

V. LABELING OF TARGETED THERAPIES AND THE CHALLENGE OF KEEPING CLINICIANS INFORMED

A. Limits of Product Labeling as an Informational Medium

Patients cannot benefit from advances in pharmacogenomics unless clinicians have good, up-to-date, practice-oriented information about which tests to use to target particular drugs, and how to translate test results into specific prescribing decisions. The Secretary's Advisory Committee on Genetics, Health, and Society (SACGHS), in its priority-setting discussions, has focused on physicians' need for practical advice on the use of pharmacogenomic data in clinical settings.⁹³ There already are cases where drugs have been relabeled to incorporate pharmacogenomic information,⁹⁴ although submission of pharmacogenomic data to FDA remains largely voluntary, with mandatory submission required only in certain instances.⁹⁵ Scientists and physicians have called for more information about genetic variability of drug response to be included in drug labeling.⁹⁶

Before making detailed decisions about when, how, and how much pharmacogenomic information should be placed in product labeling, there is a need to ask whether labeling is a good medium for communicating this information. Product labeling traditionally has been FDA's first-line medium for communicating indicated uses, instructions, and warnings to clinicians. Approval and labeling of targeted therapies have been, and continue to be, clarified through efforts by FDA's Office of *In Vitro* Diagnostic Devices (OIVD), Office of Combination Products (OCP), and Interdisciplinary Pharmacogenomics Review Group (IPRG). Despite these efforts, there may be real limits, discussed *infra*, on how informative FDA-approved product labeling is likely to be in the case of TAB tests and targeted therapies. An entirely new mechanism may be needed to ensure timely communication of information about targeted therapies to clinicians.

Wide variations in labeling already are apparent in the handful of TAB tests and targeted drugs that FDA has approved to date. There are a few examples where a drug and a TAB test are expressly cross-labeled for use together, so that the drug labeling identifies specific tests and gives information on how to vary prescribing in response to test results⁹⁷ (see Section V.D, *infra*, for more on cross-labeling). In other cases, labeling merely notes that patient response may vary based on genetic factors, but lacks specific recommendations for testing and interpretation of test results.⁹⁸ Some drugs that are

⁹³ E. Winn-Deen, *Session Overview and Goals*, SACGHS MEETING TRANSCRIPT (June 15-16, 2005), at www4.od.nih.gov/oba/sacghs/meetings/June2005/transcript/6-16_Session_Overview.pdf.

⁹⁴ Lesko & Woodcock, *supra* note 3, at 767-768.

⁹⁵ HHS, FDA, *Guidance for Industry: Pharmacogenomic Data Submissions* (Mar., 2005), at 10-11, 19-24.

⁹⁶ See, e.g., Tommy Andersson, David A. Flockhart, David B. Goldstein, *et al.*, *Drug-metabolizing Enzymes: Evidence for Clinical Utility of Pharmacogenomic Tests*, 78 CLINICAL PHARMACOLOGY & THERAPEUTICS 559, 560 (2005).

⁹⁷ See, e.g., approved package insert for trastuzumab (HerceptinTM), at <http://www.gene.com/gene/products/information/oncology/herceptin/insert.jsp>; see sections entitled *CLINICAL STUDIES: HER2 Detection* and *PRECAUTIONS: HER2 Testing*, which cross-reference package inserts for the HercepTestTM IHC assay and the PathvysionTM HER-2 DNA Probe Kit (FISH test) products.

⁹⁸ See, e.g., approved package insert for Atomoxetine HCl (StratteraTM); see sections entitled *Human Pharmacokinetics: Metabolism and Elimination*, *Drug-Drug Interactions*, and *PRECAUTIONS: Drug-Drug Interactions*, noting that the drug is metabolized primarily through the CYP2D6 enzymatic pathway and commenting on the possible need for dosage adjustment when the drug is co-administered with certain CYP2D6 inhibitors. See, also, Lesko & Woodcock, *supra* note 3, at 766 for a discussion of factors that were considered in deciding how to address gene-drug interactions in Atomoxetine labeling.

known to exhibit genetic variability of response do not yet mention this fact in labeling. Some TAB tests have been approved for use in identifying particular biomarkers that have been shown, in peer-reviewed literature, to affect drug response; it is left up to the clinician to decide how to use that test to target a particular drug.⁹⁹ Moreover, clinicians are faced with making decisions about the use of home-brew TAB tests for which no FDA-approved labeling exists.

In theory, clearer information could be provided to clinicians if FDA reviewed all TAB tests (including home-brew tests) and required specific cross-labeling of TAB tests and the drugs they target. In practice, this is unlikely to be a workable solution. It is not clear that FDA has the legal authority to compel drug and test manufacturers to cross-label their products, unless they voluntarily agree to cooperate (*see* Section V.D, *infra*). Even if FDA had this authority, cross-labeling may not be a good idea for other reasons. FDA's processes for validating and amending claims in drug labeling may be too slow, too deliberate, and too costly to keep pace with advances in this rapidly evolving field. Some advances in personalized medicine will be in the nature of discrete, substantial technological advances that, once made, remain standing for a significant period of time. It may be feasible to reflect such discoveries in drug labeling. However, many important advances will occur as a rapid sequence of infinitesimal, successive improvements (e.g., a more sensitive test that allows lethal reactions to a drug to be shaved by one or two per cent). TAB tests, like other diagnostic products, go through rapid technical evolution, often on a 12–18 month cycle, and small improvements can have life-and-death consequences for patients who would have been erroneously identified under an older TAB test. Cementing test recommendations into FDA-approved product labeling could delay the clinical uptake of new, better tests. Finally, the issue of off-label use is especially complex in the case of targeted therapies, since either the TAB test, the drug itself, or both potentially can be used off-label (*see* Section V.C, *infra*). Even if labeling provides specific instructions on how to target a drug in its indicated use, this scarcely addresses the full array of off-label uses that clinicians may confront.

If product labeling is not a good medium for providing clear, current information to clinicians, then alternative approaches may be needed. Surveys and interviews should be conducted to assess difficulties clinicians are experiencing in interpreting and applying information in the various labeling scenarios that already exist for targeted therapies. These labeling scenarios include: a) specific cross-labeling of drugs and FDA-reviewed TAB tests; b) drug labeling that provides non-specific warnings and/or information about genetic variability of patient response; and (c) drugs for which labeling does not address variability of treatment response, but for which there is other scientific evidence suggesting variability of drug response in response to particular biomarkers. These last two scenarios can be further nuanced, depending on: 1) whether FDA-cleared or approved tests are available to measure the particular biomarker that correlates with variations in drug response; 2) whether only home-brew tests are available; or 3) whether both types of test are available. For these various scenarios, key questions are: What resources are physicians currently using to draw sound clinical conclusions from this disparate information? What additional resources do clinicians feel they need (e.g., up-to-date

⁹⁹ *See, e.g.,* FDA, *New Device Clearance: Roche Amplichip CYP450 Genotyping test*, *supra* note 16. *See, generally,* HHS, FDA, *Guidance for Industry and FDA Staff: Class II Special Controls Guidance Document: Drug Metabolizing Enzyme Genotyping System* (Mar. 10, 2005), § 8, at 13–14 (providing for approval based on peer-reviewed scientific literature and other external evidence of validity and utility under certain circumstances). *See, also,* HHS, FDA, *Draft Guidance for Industry and FDA Staff: Pharmacogenetic Tests and Genetic Tests for Heritable Markers* (Feb. 9, 2006), § F, at 13 (describing conditions under which FDA may clear a new test for clinical use based on the existence of sufficient published literature establishing clinical performance).

information about the validity of particular biomarkers as tools for directing the use of particular drugs; current standards concerning the clinical claims that physicians reasonably can make about TAB tests and their usefulness in directing drug therapy; information about available TAB tests and which ones are relevant to the targeting of which drug)?

Following this assessment of clinicians' needs, the next step is to identify how best to provide the information they currently lack. Options include, for example, a set of voluntary practice guidelines and standards issued by a special-purpose TAB Clinical Standards Board formed within the medical profession and scientific community; expansion of formal regulatory activities by FDA and state medical boards; or enhanced legal duties for drug manufacturers to maintain current information about the targeting of their drugs. These last two options likely would require amendments to existing statutes and regulations, which would take time. On the other hand, standards set by a TAB Clinical Standards Board initially could be framed as voluntary medical practice guidelines and would not require statutory authorization. Implementation may be swifter, but the guidelines would lack binding legal or regulatory effect. Over time, as its standards become well established, the Clinical Standards Board could work with state and federal legislatures and regulatory bodies to have its standards formally recognized for various legal and regulatory purposes (e.g., for use in Medicare and insurance reimbursement decisions, to inform the standard of care in drug-injury lawsuits, and to determine state-law informed consent requirements in situations where administering a drug would pose special risks for a particular population subgroup). A good example of voluntary standards that have subsequently been adopted for regulatory use are the Current Procedural Terminology (CPT) billing codes, which were developed by the American Medical Association (AMA) in the 1960s and 1970s as a recommended measure to improve the consistency of medical records, but later adopted as a requirement for Medicare and Medicaid billing in the 1980s.¹⁰⁰ Each approach obviously has advantages and disadvantages and different implications that need to be carefully weighed.

B. Impact of Labeling Policy on Reimbursement, Patient Access, and Standard of Care

How targeted therapies are labeled may have important impacts on patients' rights and patients' access to needed care. These impacts need to be better understood, to ensure consistent legal treatment of functionally similar therapeutic products. Different targeted therapies may be labeled in different ways—some with specific cross-labeling of the drug and TAB test, some without, and some with only general information about genetic variability of drug response—and these differences may carry important legal and social implications.

For example, many states recognize labeling as a factor to consider in determining the standard of care.¹⁰¹ Whether products are cross-labeled could affect physicians' duty to run a TAB test before administering a drug. It also may affect preemption in state tort lawsuits. A TAB test that is part of a cross-labeled combination product may have been approved as part of the new drug application, as opposed to being separately cleared or approved under FDA's device regulations. FDA drug and device approvals may have

¹⁰⁰ AMA, *CPT Process—How a Code Becomes a Code*, at <http://www.ama-assn.org/ama/pub/category/print/3882.html>.

¹⁰¹ Linda A. Sharp, *Annotation: Malpractice: Physician's Liability for Injury or Death Resulting from Side Effects of Drugs Intentionally Administered to or Prescribed for a Patient*, 57 A.L.R. 5th 433, § 2[a] (1997, updated through 2004).

different preemptive effects under state tort law. Under the learned intermediary doctrine, the content of labeling also may affect the apportionment of liability as between product manufacturers and physicians.¹⁰²

Medicare and insurance coverage and reimbursement decisions may refer to approved indications in labeling, when establishing whether a given treatment is reimbursable. Problems with reimbursement of testing services and TAB tests pose an important potential barrier to wider clinical use of targeted therapies.¹⁰³ SACGHS has identified coverage and reimbursement of genetic technologies and services as one of the highest priority issues for analysis and deliberation.¹⁰⁴ Whether a TAB test is “reasonable and necessary” for purposes of insurance coverage and reimbursement may depend on factors such as 1) whether the drug and TAB test were approved as a combination product (*see* Section V.D, *infra*), which implies that they would be cross-labeled for use together, 2) whether they are otherwise cross-labeled, or 3) whether they are approved separately and labeled for separate use. Patients’ access to targeted therapies could thus depend on the vagaries of whether a drug and TAB test happen to be cross-labeled. Impacts on access may need to be addressed by clarifying Medicare/Medicaid and insurance regulations.

TAB tests include many different types of tests, e.g., tests to detect a particular protein in a patient’s tumor, *vs.* genetic tests that predict the patients’ ability to metabolize a particular drug. These differences also may have broader legal significance. For example, a test that establishes whether a patient’s disease has particular molecular targets (e.g., HER-2 for trastuzumab) may fall within legal concept of “diagnosis,” since HER-2 positive and HER-2 negative breast cancer are, in effect, two different illnesses. In contrast, a test that predicts a patient’s metabolic response to medicine does not fall so clearly under the notion of “diagnosis.” This difference could affect whether a physician has a legal duty under state law to order the test (e.g., whether tort case law pertaining to misdiagnosis is applicable), and it also may affect the willingness of insurers to cover the test. It may be necessary to update existing laws and regulations to clarify their application to TAB tests and targeted therapies, to avoid irrational distinctions in how functionally similar therapies are treated under the law.

C. Ethical, Legal, and Safety Issues with Off-label Use of Targeted Therapies and TAB Tests

Off-label use of medical products has long held a valid place in medical practice. It is neither feasible nor cost-effective to perform clinical trials to test every conceivable use of a new medical product. After a product has been approved by FDA, physicians are allowed to prescribe it to treat patient subgroups and health conditions, other than those for which the product has been tested, even if this means disregarding safety warnings in the product labeling.¹⁰⁵ Off-label use supports discovery of new therapeutic uses that otherwise would have gone undiscovered. Without off-label uses, population subgroups that are hard to include in clinical trials (e.g., children, the elderly, pregnant

¹⁰² Diane Schmauder Kane, *Annotation: Construction and Application of the Learned Intermediary Doctrine*, 57 A.L.R. 5th 1 (1998, updated through 2004).

¹⁰³ Institute of Medicine, *MEDICARE LABORATORY PAYMENT POLICY NOW AND IN THE FUTURE* (Dianne Miller Wolman, Andrea L. Kalfoglou, and Lauren LeRoy, eds., (2000)), at 1-3. *See, also*, The Lewin Group, *THE VALUE OF DIAGNOSTICS: INNOVATION, ADOPTION, AND DIFFUSION INTO HEALTH CARE* (July, 2005), at 5, 92-130.

¹⁰⁴ SACGHS, *DRAFT REPORT ON COVERAGE AND REIMBURSEMENT OF GENETIC TECHNOLOGIES AND SERVICES* (Jun. 14, 2004), at <http://www4.od.nih.gov/oba/sacghs/meetings/June2004/Berry.pdf>.

¹⁰⁵ Evans & Flockhart, *supra* note 7, at 48-50 (reviewing regulations and literature on off-label use).

women) might be left with few treatment options. The challenge, in setting policy, is to strike an appropriate balance between allowing off-label uses and promoting physician compliance with important instructions for use and safety warnings.

Off-label use presents especially complex issues in the case of targeted therapies. With a traditional, untargeted drug, the lack of an approved indication for use in a particular population subgroup may simply mean that the drug was never tested in that subgroup. This does not necessarily imply that the drug would be positively unsafe or ineffective if physicians prescribed it off-label for members of that subgroup. In contrast, clinical trials for targeted therapies may have excluded certain subpopulations deliberately, based on genetic or other data suggesting that the drug would be ineffective or unsafe in that subgroup. For genetically targeted therapies, the lack of an approved indication in labeling may be “with prejudice,” i.e., it may mean, “this use may be bad,” rather than merely “this use was never tested.” Another complicating factor is that targeted therapies involve the use of two products: a TAB test and a drug. “Off-label use” could mean many different things, as shown in Table 1.

Table 1: Examples of Off-label Uses of Targeted Therapies and TAB Tests

Off-label Use Scenario	Description
Off-label use of a TAB test. On-label use of the drug.	Use of a novel targeting strategy, based on unsubstantiated beliefs about the effect of particular genes or biomarkers on drug response. However, the drug is being used to treat a health condition for which the drug has been shown to be effective.
Off-label use of a drug relative to health conditions listed in its approved indications. On-label use of the TAB test.	Use of a drug to treat a health condition for which the drug has not been approved. However, a known targeting strategy is being used (e.g., the drug is known to be metabolized by the CYP-450 enzyme and is approved for use for one illness; now the drug is being used to treat a different illness but patients will still be screened to determine their CYP-450 enzyme status).
Off-label use of a drug relative to population subgroups for which its use is approved (i.e., use contrary to recommended targeting strategy).	Use of a targeted therapy in a population subgroup other than the one for which it is intended. (e.g., giving a drug that is intended for use in HER-2 positive patients to HER-2 negative patients; giving a drug to a patient who lacks enzymes for metabolizing it).
Off-label use of both the drug and the TAB test	Use of a targeting strategy that is not substantiated, to direct the use of a drug to treat a condition for which it is not approved.

These various scenarios carry different medical, legal, and ethical implications, and they may differ in terms of whether there are avenues available for FDA or state regulators to control, or at least discourage, the particular off-label use in question. It seems a safe assumption that off-label uses of both TAB tests and the drugs they target may become widespread. These uses present medical practice issues, liability issues, informed consent issues, and insurance reimbursement issues that need further study. There may be a public health need to restrict some off-label uses of targeted therapies and TAB tests, but this may present difficult implementation issues. Expanding FDA's authority to regulate off-label uses could raise concerns about the appropriate division of state and federal authority to regulate the practice of medicine. Alternatives would be to address off-label use of targeted therapies through the medical practice regulations of the fifty states, or through some alternative standard-setting institution yet to be created.

Policy decisions about off-label use of TAB tests and targeted therapies need to be informed by good data and analysis. The first step would be to characterize the various scenarios of off-label use of these products and to develop examples to aid in the analysis. For each scenario, what are the public health, ethical, legal, and economic implications? In particular, are there different implications for TAB tests that detect safety biomarkers, as opposed to biomarkers that bear on a drug's effectiveness? The second step would be to assess the pros and cons of imposing restrictions on off-label use in the special context of targeted therapies and TAB testing. Certain off-label use scenarios may be particularly wasteful (e.g., giving a drug that is known to work only on certain types of tumors to a patient who does not have that type of tumor, simply because the patient is out of treatment options and has asked to try the drug) or dangerous (e.g., ignoring a known valid safety biomarker that indicates the patient is at high risk for a serious adverse effect). Different measures may be appropriate for managing off-label uses that appear to be particularly wasteful or dangerous (e.g., allowing use with informed consent vs. banning the use altogether). Finally, there is a need to assess which regulators are best positioned to address each of these problems, and what additional statutory or regulatory authority they may need.

Many parties would benefit from a clarification of the ethical, legal, and safety issues that surround off-label use of targeted therapies. Regulators, product manufacturers, and physicians need this information to guide basic decisions about appropriate off-label uses of these new products. Attorneys and courts will need this information as they begin to encounter drug-injury suits related to the off-label use of targeted therapies and TAB tests. This information also is needed as a basis for efforts to educate the public about new or unfamiliar risks that may arise when targeted therapies are prescribed off-label.

D. Policy Issues with Cross-Labeling of Drugs and TAB Tests

Cross-labeling refers to the notion of having drug labeling cross-reference TAB tests, and vice-versa. As noted in Section V.A, *supra*, this would allow product labeling to provide clear indications for use of the drug in patient subgroups with different genes or biomarkers, along with instructions on how to use TAB tests to measure the relevant patient traits for targeting the particular drug. Cross-labeling could offer public health advantages and could facilitate introduction of new targeted therapies. However, the issue of cross-labeling has been controversial and there are merits on either side of the debate. Regulatory policies on this matter have ethical, legal, public-health and commercial impacts that need to be carefully examined.

FDA does not appear to have clear authority, under current statutes and regulations, to compel a drug manufacturer to cross-label its product for use with a TAB test made by another manufacturer.¹⁰⁶ FDA has indicated that it will pursue policies to encourage voluntary cooperation among manufacturers,¹⁰⁷ but apparently will stop short of forcing companies to cooperate against their will. Segments of the industry have voiced strong opposition to compulsory cross-labeling, citing various legal, commercial, and product-quality concerns.¹⁰⁸ Cross-labeling of products could subject one manufacturer to liability for defects in the other manufacturer's product. It could delay approval of modifications, when products undergo modernization and improvement. For business reasons, a manufacturer may not wish to be placed into a "forced marriage" with the manufacturer of a cross-labeled product. FDA's fees for amending labeling are substantial,¹⁰⁹ and the revisions necessary to effect cross-labeling take time and effort to complete. Unless manufacturers voluntarily agree to cooperate, there is presently no good mechanism to achieve cross-labeling.

Even in situations where a drug and a TAB test both are made by a single manufacturer, the question of mandatory cross-labeling has been controversial. The question of cross-labeling is tied up with the issue of whether therapies that combine a drug and a TAB test should be regulated as combination products (*see* Box 2 below). FDA's Office of Combination Products, in 2005, published a concept paper¹¹⁰ suggesting that FDA should be able to require such manufacturers to file a single combination-product¹¹¹ application in certain circumstances, rather than file separate drug and device applications for approval. Industry comments were strongly opposed to this and cited sound legal and commercial reasons why manufacturers might wish, in a given instance, to avoid cross-labeling of a drug and device as a combination product.¹¹² Similar objections were voiced in response to FDA's drug/device co-development draft concept paper,¹¹³ and FDA amended its language to make clear that co-developed drugs and TAB tests will not necessarily be treated as combination products.

A practical problem with cross-labeling is that the majority of TAB tests may continue to be non-FDA-regulated home-brew tests, which would be unsuitable for cross-labeling, since their analytical and clinical claims have not met the standard of proof required for inclusion in labeling. Yet, if drugs are cross-labeled only with FDA-approved TAB tests, this could have the effect of referencing an outdated, FDA-approved test that home-brew makers have subsequently improved.

To date, the cross-labeling issue has been debated primarily within the medical products industry. There needs to be a wider, more inclusive discussion of public-health as well as business impacts of cross-labeling policy. Fair consideration should be given to

¹⁰⁶ FDA/DIA WORKSHOP: COMBINATION PRODUCTS AND MUTUALLY CONFORMING LABELING (May 10, 2005), at http://www.fda.gov/oc/combination/presentations/dia/dia05_10.html. *See*, Presentation of Nancy Stadel, Office of the Chief Counsel, FDA, *Legal Considerations in Cross Labeling Policy*; Presentation of Suzanne O'Shea, Office of Combination Products, FDA, *Perspectives on Cross Labeling*.

¹⁰⁷ *Id.*

¹⁰⁸ FDA/DIA WORKSHOP, *supra* note 106, *see, e.g.*, Presentation of Anna Longwell, Roche Diagnostics, *FDA's Role in Encouraging Innovation in Combination Products*; Presentation of David Eveleth, Pfizer, Inc., *Combination Products and Mutually Conforming Labeling*.

¹⁰⁹ HHS, FDA, *Prescription Drug User Fee Rates for Fiscal Year 2007*, 71 Fed. Reg. 43,780, 42,784 (Aug. 2, 2006); *Medical Device User Fee Rates for Fiscal Year 2007*, 71 Fed. Reg. 43,784, 43,785 (Aug. 2, 2006).

¹¹⁰ HHS, FDA, *Request for Comments on Concept Paper: Number of Marketing Applications for Combination Products* (Sept., 2005), at <http://www.fda.gov/oc/combination/reqcomm905.html>.

¹¹¹ As defined in 21 CFR 3.2(e).

¹¹² *See, e.g.*, Combination Products Coalition, Comments on Concept Paper: Number of Marketing Applications for a Combination Product (Docket No. 2005N-0098) (Nov. 15, 2005), at: www.combination-products.com/images/Comments_FDA_111505.pdf.

¹¹³ HHS, FDA, *Drug-Diagnostic Co-Development Concept Paper* (Apr., 2005), *supra* note 13.

the “pros” of providing FDA greater authority to require cross-labeling of drugs and TAB tests in specific situations where the case for mandatory cross-labeling is strongest (e.g., situations where failure to cross-label products poses serious patient-safety issues). The “cons” also demand careful consideration (e.g., lags in updating labeling to reflect new technologies; problems in apportioning liability among manufacturers; the possibility of constitutional “takings” problems if manufacturers are forced into unwanted business relationships). If mandatory cross-labeling is not a workable policy option, then the debate returns to the question of what alternative measures may be needed, to provide clear instructions and warnings to clinicians (*See* Section V.A *supra*).

Box 2. Targeted Therapies May or May Not be Combination Products

FDA’s regulations at 21 CFR 3.2(e) define combination products, which are products that combine a medical device (such as a genetic test), a drug, and/or a biologic. A targeted therapy, which uses a genetic test to inform the prescribing of a drug, may or may not fit within FDA’s definition of a “combination product.” Whether it does has important implications for the labeling of the targeted therapy—i.e., what labeling information will be available to help physicians understand how to use the targeted therapy. It also affects the approval pathway and other regulatory requirements that will apply to the targeted therapy.

Even though the drug and the test are packaged separately, they may still qualify as a combination product, but only if certain conditions are met: The labeling of one of the products must indicate that it is intended for use only with an “approved individually specified” second product, where both are required to achieve the intended use, indication, or effect.¹¹⁴ Moreover, if the two products are FDA-approved at different times, the second approval would necessitate a change in the labeling of the first product.¹¹⁵

Thus, if a drug’s labeling specifically indicates that the drug is for use with an FDA-approved test, which is individually specified, the pair would be a combination product. The meaning of “individually specified” has not yet been clarified but is thought to require reference to a specific test by its proprietary name.

Examples of Targeted Therapies That are Not Combination Products

- A drug’s indicated use is in patients with a certain genotype or biomarker, but the drug’s labeling does not name a specific test to use
- A drug’s indicated use is in patients with a certain genotype or biomarker, but the needed test is not FDA-approved and is a CLIA-regulated home-brew test
- Drug labeling merely notes that genetic variation in drug response has been observed.

VI. COOPERATIVE DISCOVERY AND DEVELOPMENT OF TARGETED THERAPIES

A. Reducing Barriers to Cooperative Discovery and Development

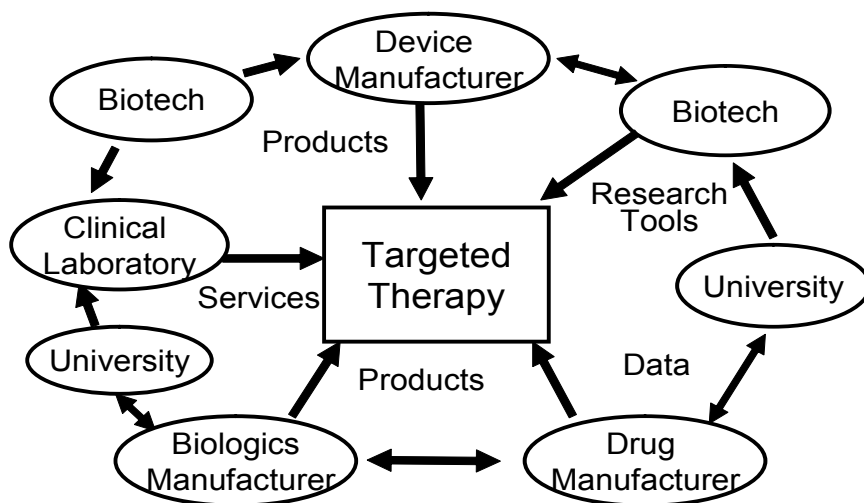
In pharmacogenomics, the linear product-development pipeline often is supplanted by a “spider web” in, which new products emerge from interlinked contributions of

¹¹⁴ 21 CFR 3.2(e)(3).

¹¹⁵ *Id.*

many different parties, as depicted in Figure 5. Developing a single targeted therapy may require inputs from diverse sources: a drug or biologic product; a genetic test for screening patients' probable response to that product; clinical laboratory services; tissue resources, genetic and clinical information, research tools, and algorithms for use in discovering and validating the targeting strategy. Essential inputs often are held by separate commercial and non-commercial entities and may be subject to patent, copyright, trade-secret, and/or contractual protections. Discovering targeted therapies and translating them into clinical use requires that inputs flow together in new ways, i.e., that separate entities cooperate.

Figure 5
Cooperative Model of Product Development



Since the early phases of the Human Genome Project, there has been concern that intellectual property rights have the potential to impede cooperation that is needed to develop clinically useful therapies.¹¹⁶ The NIH has provided substantial funding under its Ethical, Legal, and Social Issues program to examine impacts of gene patents and other IP protections that restrict access to data and research tools. NIH also has provided leadership through its guidelines for technology licensing, data sharing, and research material exchanges. These measures have helped allay concerns that IP rights may block clinical translation in pharmacogenomics.

An equally disturbing prospect is that non-cooperating parties may be able to engage in a wide variety of other strategic blocking behaviors based not on IP rights, but on powers and rights the parties may have under other laws and regulations. The Health Insurance Portability and Accountability Act of 1996 (HIPAA)¹¹⁷ privacy regulations¹¹⁸ and regulations for protection of human research subjects¹¹⁹ have an important, intended purpose—to protect people who have donated their tissues and health information for

¹¹⁶ See, e.g., National Research Council, REAPING THE BENEFITS OF GENOMIC AND PROTEOMIC RESEARCH: INTELLECTUAL PROPERTY RIGHTS, INNOVATION, AND PUBLIC HEALTH (Stephen A. Merrill & Anne-Marie Mazza, eds., (2006)). See, generally, M.A. Heller & R.S. Eisenberg, *Can patents deter innovation? The Anticommons in Biomedical Research*, 280 SCIENCE 698 (1998). See, also, L.B. Andrews, *The Gene Patent Dilemma: Balancing Commercial Incentives With Health Needs*, 2 Hous. J. HEALTH L. & POL'Y 65 (2002).

¹¹⁷ HIPAA, Pub. L. No. 104-191, 110 Stat. 1936 (1996) (codified in scattered sections of the U.S.C.).

¹¹⁸ 45 C.F.R. Parts 160, 164.

¹¹⁹ 45 C.F.R. Part 46; 21 C.F.R. Parts 50, 56.

medical research. They should not be allowed to become mere pretexts by which manufacturers can block flows of data and tissues that might allow third parties to improve the targeting of existing drugs. Finding ways to protect trial participants and tissue donors, while still promoting information flows that are critical to the development of targeted therapies, will be a crucial challenge in coming years.

Other “regulatory-blocking” behaviors could include, for example, taking advantage of features of existing FDA regulations to delay a third party in moving new or better targeting strategies to patients. FDA regulations rely heavily on the concept of a unitary product sponsor (either an individual company or a cooperating group of companies). The FDCA and FDA regulations grant the sponsor significant discretion to make elective choices that affect how a given medical product will be regulated in the future. For example, the sponsor of a targeted therapy, consisting of a drug to be used together with a genetic test, may choose to seek approval of the drug and test as a cross-labeled combination product,¹²⁰ in which case the pair seemingly would have a “drug” primary mode of action and be regulated, together, as a drug.¹²¹ However, the sponsor may elect to pursue a separate device clearance or approval for the test, in addition to seeking the required drug approval for the drug/device combination product.¹²² A third alternative is to seek separate device and drug approvals for non-cross-labeled use. These choices may affect the ease with which a third party later can seek a 510(k) clearance¹²³ for a similar test (using the original test as the predicate device), as opposed to having to seek a premarket approval for the new test (if no other predicate device exists).¹²⁴ The ability to use a 510(k) clearance, rather than a premarket approval, can mean a significant reduction in the cost, time, and data requirements for moving the newer test to market. Elective choices by individual manufacturers affect the barriers to entry faced by other product developers. Such choices, in most cases, are driven by individual business concerns and are not driven by any nefarious intent to erect entry barriers to exclude competitors; however, this latter potential does exist and needs to be better understood.

Targeted therapies, in many cases, will flow from complex, multi-party interactions that existing regulations did not envision. Unless the necessary parties can be induced to cooperate, beneficial therapeutic concepts may lack clear pathways for FDA approval and postmarket regulation. Even when parties desire to cooperate in their dealings with FDA, they may face other barriers to cooperation, for example, under antitrust law or under the HIPAA privacy regulations. Discoveries by third parties (i.e., parties other than the drug manufacturer) may be essential to better targeting of therapies, since there may be little economic incentive for the drug manufacturer to explore new targeting strategies that would reduce drug sales by screening out non-responding patients.¹²⁵ Adverse responders (people who are injured by a drug) confront manufacturers with a risk of lawsuits, but non-responders (who do not benefit, but are not directly injured) pose little threat of litigation under current tort doctrines.¹²⁶ Non-responders are a source of sales revenue with little litigation risk; what incentive is there to invest in research to screen them out? Third parties, including academic researchers and independent test

¹²⁰ 21 C.F.R. § 3.2.

¹²¹ HHS, FDA, *Definition of Primary Mode of Action of a Combination Product: Final Rule* [Docket No. 2004N-0194], 70 Fed. Reg. 49,848-49,862 (Aug. 25, 2005); see definitions at 21 C.F.R. 3.2(k),(m).

¹²² FDA, Office of Combination Products, *Concept Paper: Number of Marketing Applications for a Combination Product*, at <http://www.fda.gov/oc/combinations/singlesepconpaper.html>, see section entitled, *When might FDA accept two marketing applications when a single application would be sufficient?*

¹²³ 21 C.F.R. Part 807, Subpt. E, §§ 807.81 – 807.100.

¹²⁴ 21 C.F.R. Part 814.

¹²⁵ Evans *et al.*, *supra* note 3, at 1289.

¹²⁶ *Id.*

developers, may ultimately be the most prolific source of new discoveries of how to target existing drugs (*See* Section II, *supra*, at Scenario III). Without cooperation of the drug developer, it may not be possible for these independent test developers to cross-label their tests for use with specific drugs (*See* Section V.D, *supra*). In some cases, it may not be possible to bring the tests to market at all (cross-labeled or not), without access to proprietary data held by the drug manufacturer.

There are occasional allegations of blocking behaviors, many of them arising when a small test developer is rebuffed in an attempt to interest a large drug manufacturer in a product-development co-venture.¹²⁷ The frequency of these problems has not been systematically examined, nor are the reasons well enough understood to assess whether anything improper is occurring. A rebuff could, for example, reflect honest differences in business judgment about the attractiveness of the co-venture or valid concerns about apportionment of product liability; it does not necessarily imply a more sinister motive to preserve market share at the expense of non-responding patients. Policymakers and participants in the medical products industry need basic, empirical information: Are there grounds to suspect that improper blocking behaviors actually are occurring? If so, which specific provisions of current laws and regulations lend themselves to blocking behaviors in multiparty discovery and development scenarios? Can laws and regulations be modernized in a way that reduces this potential? If the alleged blocking behaviors reflect legitimate concerns about apportionment of liabilities for drugs and tests that are used together, then how can liability issues be resolved for cooperatively developed therapies?

The “big picture” here is this: Pharmacogenomics requires a difficult balancing of public and private interests—the public’s interest in reducing drug-related injuries through improved targeting *vs.* the interest of drug developers in controlling the destiny of their own proprietary know-how and products. The drug, biologics, and medical device industries in the United States have long operated under a competitive business structure, and it is inevitably controversial to suggest that these industries may exhibit utility-like characteristics. Without questioning the competitive model for the industry as a whole, it is fair to ask whether this traditional business model is optimal for the particular subset of industry activities that relate to pharmacogenomics. Discovery and validation of biomarkers that affect drug response, viewed as a business pursuit, exhibit strong “natural monopoly” characteristics, not unlike those seen in public utility industries like electric power transmission. In particular, duplicative investments to discover and validate the same biomarker add little social value and there are economies of scale to a large, networked discovery effort in which information and data are widely shared. Standardization may offer real benefits (e.g., there would be less confusion in applying TAB tests if physicians had one rather than multiple tests for a given biomarker). On the other hand, standardization is often the enemy of innovation and improvement. The optimal structure for pharmacogenomic activities—cooperative *vs.* competitive—can be argued either way. At present, this debate has scarcely begun.

The recent formation of an industry group to cooperate in the validation of drug safety biomarkers¹²⁸ is an example of a voluntary effort by companies to work together. The United States may decide, for many good reasons, not to pursue policies that would make intra-industry cooperation mandatory. However, short of that, there may be advantages in simply reducing the barriers to voluntary cooperation. The first step would

¹²⁷ U.K. Pharmacogenetics Study Group, POLICY ISSUES IN PHARMACOGENETICS: A POLICY BRIEFING FROM THE U.K. PHARMACOGENETICS STUDY GROUP (July, 2006) 4,5, at <http://www.york.ac.uk/res/pgx/publications>.

¹²⁸ FDA, *FDA and the Critical Path Institute Announce Predictive Safety Testing Consortium* (News release P06-40, (Mar. 16, 2006)).

be to identify the potential barriers (e.g., antitrust concerns; HIPAA constraints on sharing of data; aspects of human-subject protection regulations such as requirements for specificity of consent to future uses of stored tissues; disparities between FDA and Common Rule human-subject protections and other harmonization problems that make it hard for separate entities to mesh their respective research programs).¹²⁹

A related issue is the appropriate ownership structures for discoveries made through cooperative efforts in pharmacogenetics and molecular targeting of therapies. These discoveries carry significant implications for public health, since badly targeted therapies can harm patients; this would weigh in favor of public ownership as a shared resource. However, significant private investments are required to make these discoveries, and investment may dry up if legitimate private interests are not protected. A major question in coming years will be, "What is the appropriate balance of public and private interests in pharmacogenomics and what are the various policy options through which it can be achieved?" Pharmacogenomics is a paradigm-shifting technological change that may require a rethinking of old business structures and regulatory assumptions.

B. Redefining the "Finished" Medical Product in the Age of Pharmacogenomics

In principle, the risk-benefit characteristics of any drug can be improved through subsequent discovery of molecular or pharmacogenetic targeting strategies. The most obvious candidates are drugs that have a narrow therapeutic range, wide inter-individual variability in dosing requirements, and frequent and serious safety problems.¹³⁰ To reap the full clinical benefits of pharmacogenomics, the United States needs to foster and stimulate this form of "successive improvement" activity. Current law and regulations were not designed with this as a goal.

Postmarket pharmacogenomic discovery (*See* Section II, *supra*, at Scenario III) alters the very concept of a finished medical product, which is implicit in FDA's current regulatory approval paradigm. Current regulations view approved drugs as finished products, rather than as intermediate raw materials to which additional value is yet to be added. FDA approves a drug based on a particular risk-benefit ratio, often evaluated in clinical trials in an unscreened population of trial participants. FDA has little authority to require postmarket studies aimed at improving this risk-benefit ratio, and current regulations lack an effective cost-spreading mechanism to aid product sponsors in recovering the costs of such studies from all the parties who stand to gain from improved targeting.¹³¹ As a result, current regulations do little to promote successive improvement of the risk-benefit ratio by drug manufacturers. Moreover, current regulations put obstacles in the path of third parties who might try to make such improvements to other manufacturers' drugs. Third-party researchers may lack access to data that would be needed to validate a targeting strategy for an approved drug and, even if they succeed in validating a new targeting strategy, cross-labeling of the drug and TAB test may not be possible (*See* Section V.D, *infra*).

Pharmacogenomics fundamentally challenges the notion that an FDA-approved drug is a finished product. An untargeted drug—a drug that has been approved by

¹²⁹ *See, generally*, B.J. Evans, & E.M. Meslin, *Encouraging Translational Research Through Harmonization of FDA and Common Rule Informed Consent Requirements for Research with Banked Specimens*, 27 JOURNAL OF LEGAL MEDICINE 119 (2006).

¹³⁰ Lesko & Woodcock, *supra* note 3, at 767.

¹³¹ Evans & Flockhart, *supra* note 7, at 47 (discussing limits of FDA's authority to require postmarket studies and other measures to improve the risk-benefit characteristics of a drug after its approval).

FDA but which exhibits significant individual variation in patient response—is but a work in progress. Pharmacogenomic research may be able to take this untargeted drug and turn it into a targeted drug, by discovering screening strategies that let the drug be prescribed more selectively for subgroups of patients who are likely to experience its benefits but not its risks. The targeted version of the drug is, in effect, a successor product, distinguished by an entirely new risk-benefit ratio. It is a jet, rather than a propeller biplane. The question is, “Who should have the right to be involved in making that improvement—only the original manufacturer or other parties; and if other parties may participate, when and on what terms?”

It is a matter of national importance to promote adequate investment in postmarket research to make successive improvements to existing drugs. This task will require mobilization of both public and private investment. Much of this research is in the nature of basic science, rather than product-specific research (e.g., basic genetic research and research into drug-metabolic pathways).¹³² Research to improve the targeting of one drug may produce information relevant to other drugs, creating a free-rider problem as manufacturers wait for others to take the lead. This may impede private investment, and federal funding agencies such as the NIH may need to provide leadership, both in setting research priorities and in funding the research. Public funding for this research, at present, is quite limited.

FDA also has an important role to play, by pursuing policies that will improve the incentives for private investment in this research. There is a tendency, in the pharmaceutical industry and among policymakers, to think of postmarket research in product-specific terms, e.g., FDA’s postmarket study requirements are aimed at answering specific questions about the safety or effectiveness of a particular product. Pharmacogenomics demands that policymakers adopt a wider vision of the role of research in the postapproval phase of product life. How can existing products be improved, and what needs to be done to attract adequate levels of public and private investment to make it happen? Legislative action may be needed to authorize appropriate cost-spreading mechanisms, so that the costs of postmarket research can be shared fairly among public and private sources, including all that stand to benefit from better targeting (such as physicians, patients, and insurers, as well as drug manufacturers).¹³³

To reap the true promise of personalized medicine, the United States needs to promote successive improvement of existing drugs, whether by the drug manufacturer or by other parties in the webbed network of pharmacogenomic discovery and development. A major challenge will be to balance the interests of all the parties concerned, including drug manufacturers, so that there are healthy incentives both for the initial development of new drugs, and for successive improvement of these products. Third-party improvements raise difficult issues about the rights of drug manufacturers to control the subsequent development of their products, versus the public’s interest in promoting better targeting of existing drugs. The legitimate proprietary interests of the original drug manufacturer must be protected, to ensure a healthy pipeline of new drugs.

On the other hand, reasonable limits must be placed on the power drug manufacturers have to block successive improvements by third parties. Drug manufacturers have long taken the position that they should have the right to use other parties’ patented research tools and upstream discoveries in drug-development research, so that these

¹³² *Id.* at 51.

¹³³ Evans & Flockhart, *supra* note 7, at 54-57, 62.

discoveries can be translated into new drugs that benefit patients.¹³⁴ Turnabout may be fair play. The same policy arguments that justify drug manufacturers' use of other people's upstream research tools in drug development—i.e., that it is in the public interest to bring new therapies to patients—may apply with equal force, when a third party desires to improve the targeting of an existing drug. FDA-approved drugs are now just one more “upstream” discovery—one more upstream “tool,” as it were—on the road to developing finished, targeted therapies. Striking a fair balance may require new and novel concepts. One of these would be to introduce “improve-it-or-lose-it” provisions that grant drug manufacturers a set period of time, for example, three to five years, to improve the targeting of their drugs following initial approval. During this period, manufacturers would be granted significant power to block cross-labeling of their drug products with TAB tests developed by third parties. However, at the end of this period, third parties would enjoy increased rights to cross-label their TAB tests with existing drugs, if the drug manufacturer has failed to improve drug targeting.

Less controversial reforms may include simple steps to reduce the barriers to voluntary cooperation between drug manufacturers and third-party developers of targeting tests. Much remains unclear, and legal uncertainty has a chilling effect on multi-party development and marketing of new targeted therapies. How will liabilities be apportioned; how will adverse events be reported; does the rate of treatment failure (lack of effectiveness) need to be systematically reported and disclosed to physicians or patients; how will advertising and promotion work for targeted therapies that involve a drug and a TAB test that were not developed in a cooperative setting? Under what circumstances will a TAB test that works with an innovator drug require separate validation for use in targeting generic versions of that same drug? When a drug undergoes significant changes, such as a change in formulation, should notice be provided to makers of TAB tests and to clinicians, so that they can be advised to re-validate their targeting strategies? Each of these examples raises complex issues in itself, and they are but a few examples. Targeted therapies are a relatively new phenomenon, and many of the postmarket regulatory issues they present have yet to be encountered. Postmarket regulation will be all the more complex in future years, as successive improvement activities become a more routine and expected phase of the drug development process.

VII. CONCLUSION

Two central policy problems in pharmacogenomics are, first, to establish a framework for developing, assessing, and approving the tests that will be used for targeting of therapies and, second, to promote the appropriate use of these tests in day-to-day clinical decisionmaking. These matters are closely interrelated and successful clinical translation of pharmacogenomics requires attention to both. In addition to FDA, other parties—such as the medical profession, the scientific community, and state medical boards—also have important roles to play, and these roles need to be more thoroughly

¹³⁴ See, e.g., Amicus Curiae briefs submitted in support of the Petitioner in the case *Merck KGAA v. Integra Lifesciences I, LTD*, 545 U.S. 193 (2005): *Brief for the United States as Amicus Curiae Supporting Petitioner*, 2005 WL 429972, at 23 (arguing that a narrow reading of the exemption from patent infringement in 35 U.S.C. § 271(e)(1) would harm public health by deterring research to establish the safety and effectiveness of new drugs); *Brief of Amici Curiae Eli Lilly and Company, Wyeth, and Pfizer Inc in Support of Petitioner*, 2005 WL 435888, at 13, 17, (arguing that a broad reading of the § 271(e)(1) exemption that includes upstream “tool patents” is necessary to effect Congressional intent to promote timely development of new drugs); *Brief of Amici Curiae Genentech, Inc. and Biogen Idec, Inc. in Support of Petitioner*, 2005 WL 435893, at 3 (arguing that a broad reading of the § 271(e)(1) exemption from patent liability for testing and evaluation of new drugs is necessary to encourage innovation).

elaborated. Novel approaches, and perhaps entirely new regulatory bodies and institutions, may be required.

A larger question we, as a society, need to be asking is, “What do we want pharmacogenomics and personalized medicine to *be*, once the underlying science matures?” Do we want personalized medicine to be the standard of care, so that physicians, pharmaceutical companies, and clinical laboratories face suits for drug-related injuries that might have been genetically predicted and avoided? Should pharmacogenomics instead have an exculpatory significance, so that the patient rather than the doctor or manufacturer bears responsibility for injuries that can be traced to “personal weaknesses” in the patient’s own genome? This already is being argued both ways. Will genetic screening be just another unenforceable provision of FDA-approved labeling in a world where physicians long have had discretion to disregard indications, warnings, and instructions and prescribe medical products off-label? Will pharmacogenomics make its way into state medical practice standards, with doctors facing disciplinary action for recklessly prescribing drugs without first ordering the “right” genetic tests? More fundamentally, who is going to decide what the right tests are? How we answer these questions—and many others beside them—will define what the clinical utility of pharmacogenetic testing turns out to be.

Science is more nimble than the legal constructs with which people hope to constrain it and channel it in beneficial directions. Pharmacogenomics and targeted therapies—as a science, as an element of medical practice, and as a focus of industrial and commercial activity—present novel issues that ultimately may require major changes to existing laws and regulations, which were designed with an earlier generation of medical products in mind. This article has sought to stimulate discussion about what should be included on the checklist of regulatory issues that must be resolved, if personalized medicine is to become a common clinical reality. Once there is consensus on what the problems are, the debate over solutions will undoubtedly be contentious, but that does not mean the debate can be deferred. The science is dictating the timing.